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REVIEW ARTICLE

The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of Multiple Myeloma: An Evidence-Based Review

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ABSTRACT

Evidence supporting the role of hematopoietic stem cell transplantation (SCT) in the therapy of multiple myeloma (MM) is presented and critically evaluated in this systematic evidence-based review. Specific criteria were used for searching the published medical literature and for grading the quality of the evidence, the strength of the evidence, and the strength of the treatment recommendations. Treatment recommendations based on the evidence presented in the review were made unanimously by a panel of MM experts. Recommendations for SCT as an effective therapy for MM include the following: SCT is preferred to standard chemotherapy as de novo therapy; SCT is preferred as de novo rather than salvage therapy; autologous peripheral blood stem cell transplantation (PBSCT) is preferred to bone marrow transplantation (BMT); and melphalan is preferred to melphalan plus total body irradiation as the conditioning regimen for autologous SCT. Recommendations that SCT is not effective include the following: current purging techniques of bone marrow. Recommendations of equivalence include the following: PBSCT using CD34+ selected or unselected stem cells. No recommendation is made for indications or transplantation techniques that have not been adequately studied, including the following: SCT versus standard chemotherapy as salvage therapy, tandem autologous SCT, autologous or allogeneic SCT as a high-dose sequential regimen, allogeneic BMT versus PBSCT, a preferred allogeneic myeloablative or nonmyeloablative conditioning regimen, and maintenance therapy post–autologous SCT with interferon alpha post-SCT. The priority area of needed future research is maintenance therapy posttransplantation with nothing versus interferon alpha versus other agents such as corticosteroids or thalidomide or its derivatives.

KEY WORDS

Multiple myeloma • Systematic review • Stem cell transplantation

INTRODUCTION

The American Society for Blood and Marrow Transplantation (ASBMT) in 1999 began an initiative to sponsor evidence-based reviews of the scientific and medical literature for the use of blood and marrow transplantation in the therapy of selected diseases. The first review of diffuse large cell B-cell non-Hodgkin's lymphoma (DLCL) was published in *Biology of Blood and Marrow Transplantation* in 2000 [1]. The steering committee that was convened to oversee the projects invited an independent panel of disease-specific experts to conduct each review.

The following is the second review to result from this initiative. Its goals are as follows: (1) to assemble and critically evaluate all of the evidence regarding the role of cytotoxic therapy with hematopoietic stem cell transplantation (SCT) in the therapy of multiple myeloma (MM); (2) to make treatment recommendations based on the available evidence; and (3) to identify needed areas of research.

The published literature was graded in a systematic manner on the quality of design (Table 1) and the strength of the evidence (Table 2). Treatment recommendations subsequently

Table 1. *Grading the Quality of the Evidence*

1	Evidence obtained from at least one properly randomized controlled trial
2-1	Evidence obtained from well-designated, controlled trials without randomization
2-2	Evidence obtained from well-designated, cohort or case-controlled analytic studies, preferably from more than one center or research group
2-3	Evidence obtained from multiple timed series with or without the intervention, or from dramatic results in uncontrolled experiments
3	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
4	Evidence inadequate owing to problems of methodology, eg, sample size, length or comprehensiveness of follow-up, or conflict in evidence

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were graded based on the quality and strength of the evidence (Table 3). The treatment recommendations of the expert panel are detailed in Table 4.

LITERATURE SEARCH METHODOLOGY

PubMed, the web site developed by the National Center of Biotechnology Information (NCBI) at the National Library of Medicine of the National Institutes of Health, was searched using the search terms "multiple myeloma" and "transplant." Search results were limited to those studies with human subjects that were published in the English language between January 1, 1980 and June 1, 2002. In addition, search results were excluded if they were not peer-reviewed reports or if they were editorials, letters to the editor, case reports (<10 patients), phase I (dose escalation or dose finding) studies, reviews, consensus conference reports, or practice guidelines, or if they did not focus on an aspect of cytotoxic therapy with SCT for the treatment of MM (eg, were reports of renal transplantation due to renal failure in MM patients or otherwise did not focus on an aspect of cytotoxic therapy with SCT for the treatment of MM). Abstracts and presentations at national or international meetings also were not included as evidence in this review due to their lack of formal peer review, their limited availability of details on study design and results, and because they usually are presented as preliminary, not final, analyses of clinical trial data.

QUALITATIVE AND QUANTITATIVE GRADING OF THE EVIDENCE

The hierarchy of evidence, including a grading scheme for the quality of the evidence, strength of the evidence, and strength of each treatment recommendation, has been established and published as an editorial policy statement in *Biology of Blood and Marrow Transplantation* [2]. Tables 1 to 3 are reprinted from the policy statement and define criteria used to grade the studies included in the review and the treatment recommendations. Study design, including sample size, patient selection criteria, duration of follow-up, and treatment plan, also was considered in evaluating the studies. All data in the text and tables were abstracted from the original articles first by one author (T.H.), then were double checked for accuracy and clarity by another author (P.L.M.) and at least two additional reviewers (see Acknowledgments). In some articles there were discrepancies within the data reported, ie, the median follow-up reported in the abstract was not the same as the results section or data presented in a table did not agree with those in the text. In these cases, the data most consistent with the text of the article were presented in this review. The first author (T.H.) takes responsibility for any errors that remain. Clinical studies were summarized with enough detail to give a concise summary of study design, sample size, eligibility criteria, treatment schedule, duration of follow-up, and outcomes measured. Subjective statements, such as short versus adequate versus long follow-up, small versus large sample size, and improper or inappropriate study design, were not used so that the reader is not biased by the authors' opinions.

Appendix A lists the common abbreviations used in this review. BMT refers to bone marrow transplantation, PBSCT refers to peripheral blood stem cell transplantation, and SCT refers to the general term stem cell transplantation including BMT and/or PBSCT, de novo therapy refers to only one chemotherapy regimen given before stem cell mobilization and transplantation, and salvage therapy refers to 2 or more chemotherapy regimens given before stem cell mobilization and transplantation.

Table 2. *Grading the Strength of the Evidence*

1	Experimental therapy significantly better ($P < .05$)
2	Trend in favor of experimental therapy ($P > .05$)
3	No apparent statistical effect
4	Trend favoring control group ($P > .05$)
5	Control group significantly better ($P < .05$)

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Table 3. *Grading the Strength of the Treatment Recommendation*

1	Effective treatment
2	Marginally effective treatment
3	Not an effective treatment
4	Equivalent treatments (no statistical or clinical difference between therapies)
5	Inadequately evaluated treatment and recommended for comparative study
6	Inadequately evaluated treatment but not recommended for comparative study

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TREATMENT RECOMMENDATIONS

The strength of this review is the detail conveyed in the text and the study comparisons in the summary tables at the end of major sections. Table 4 contains the summary of the treatment recommendations made by the MM expert panel. Subsequent sections of the review present the detailed descriptions of the strengths and weaknesses of the evidence and are specific to each treatment recommendation. Additional sections describe other limitations of this review, SCT costs, MM response criteria, additional ongoing studies, areas of needed research, and future initiatives.

Table 4. *Summary of Treatment Recommendations Made by the Expert Panel for Multiple Myeloma*

Indication for SCT	Treatment Recommendation*	Highest Level of Evidence†	Reference No.‡	Comments
SCT vs. standard chemotherapy as de novo therapy	1	1	3	Ongoing trials may change the recommendation.
SCT vs. standard chemotherapy as salvage therapy	5	2	10	There is only 1 non-randomized study that applies.
SCT as de novo vs. salvage therapy	2	1	13	These are equivalent in terms of overall survival, however, SCT as de novo is preferred because it may avoid the inconvenience, cost, and risk of myelodysplasia from conventional alkylating agent therapy.
Autologous vs. allogeneic SCT	2	2	17-24	Autologous SCT is recommended over a myeloablative allogeneic SCT.
Autologous PBSCT vs. BMT	1	2, 3	49-50	PBSCT is preferred based on level 2 evidence regarding engraftment, not survival, outcomes. PBSCT is also the accepted standard based on expert opinion.
Autologous CD34+ selected vs. unselected PBSCT	4	1	51-52	
Autologous purged BMT	3	2	65-68	
Tandem autologous PBSCT	6	4		A level 1 evidence study has been conducted and will soon be published to address this critical question.
Preferred autologous SCT myeloablative conditioning regimen	1	1	73	Mel is preferred to Mel plus TBI based on toxicity not efficacy, however, there is no level 1 evidence comparing Mel or Mel plus TBI with other conditioning regimens (eg, BuCy, BuMelTt).
Autologous high-dose sequential regimen	6	4	92-93	
Allogeneic BMT vs. PBSCT	6	2	130	
Preferred allogeneic SCT myeloablative conditioning regimen	5	4	131	There is only 1 feasibility study with a small sample size and no comparison group.
Allogeneic SCT nonmyeloablative regimen	5	4	132	There is only 1 feasibility study with a small sample size and no comparison group.
Allogeneic high-dose sequential regimen	6			No evidence.
Autologous SCT followed by allogeneic SCT	5			No evidence published. A study is in progress to address this question.
Maintenance therapy post-autologous SCT with IFNa vs. none	5	4	138	Early survival advantage (4-5 y) that is lost over time; problems with study methodology.
Maintenance therapy post-autologous SCT with IFNa vs. other therapies (ie, corticosteroids, thalidomide, or its derivatives)	5			No evidence.

*Definitions: 1, effective treatment; 2, marginally effective treatment; 3, not an effective treatment; 4, equivalent treatments (no statistical or clinical difference between therapies); 5, inadequately evaluated treatment and recommended for comparative study; and 6, inadequately evaluated treatment but not recommended for comparative study.

†Definitions: 1, evidence obtained from at least one properly randomized controlled trial; 2, evidence obtained from well-designated, controlled trials without randomization, cohort, or case-controlled analytic studies or multiple timed series with or without the intervention; 3, opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees; and 4, evidence inadequate owing to problems of methodology, eg, sample size, length or comprehensiveness of follow-up, or conflict in evidence.

‡The references listed represent the highest level of evidence used to make the treatment recommendation and are not inclusive of all evidence described in the review.

TRANSPLANTATION VERSUS CHEMOTHERAPY

Table 5 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcome measures for the articles detailed in this section.

De Novo

Attal et al. compared autologous BMT after 4 to 6 alternating cycles of vincristine, melphalan, cyclophosphamide, and prednisone (VMCP) and carmustine (BCNU), vincristine, adriamycin and prednisone (BVAP) (n = 100) versus conven-

Table 5. *Comparison of Patient Characteristics and Outcomes from Articles Included in Transplantation versus Chemotherapy Section*

Reference	Quality of Evidence*	Number of Patients in Study	Upper Age Limit (Median)	% DS Stage III	TRM	Median F/U (mos)	Strength of Evidence—OS*	Median OS (mos)	Strength of Evidence—EFS*	Median EFS (mos)
De Novo										
Attal et al. [3]	I	Chemo 100 BMT 100	Chemo 65 (58 mean) BMT 65 (57 mean)	Chemo 77% BMT 72%	Chemo 5% BMT 7%	Chemo 37 BMT 41	I†	Chemo 37.4 BMT NYR	I‡	Chemo 18 BMT 27
Barlogie et al. [4]	2-2	Chemo 116 SCT 123	70	NS	Chemo NS SCT 4%	31	I‡	Chemo 48 SCT NYR (62+)	I‖	Chemo 22 SCT 49
Lenhoff et al. [5]	2-2	Chemo 274 BMT 274	Chemo 60 (54) PBSCT 60 (51)	Chemo 56% PBSCT 70%	Chemo NS PBSCT 4%	Chemo NS PBSCT 32	I§	Chemo 44 PBSCT NYR	NC	Chemo NS PBSCT 27
Palumbo et al. [6]	2-2	Chemo 71 BMT 71	Chemo 75 (NS) PBSCT 75 (NS)	Chemo 72% PBSCT 75%	Chemo 4% PBSCT 0%	Chemo 39.4 PBSCT 30	I‡	Chemo 48 PBSCT NYR (56+)	I§	Chemo 17.7 PBSCT 27
Alexanian et al. [7]	2-2	Chemo 68 SCT 50	Chemo 60 (53) SCT 60 (49)	NS	Chemo NS SCT 7%	NS	3	NS	NC	NS
Gianni et al. [9]	2-2	Chemo 19 SCT 13	Chemo 61 (54) SCT 59 (50)	Chemo 42% SCT 92%	Chemo NS SCT 8%	Chemo NS SCT 36	I‡	Chemo 14 SCT 41	NC	NS
Salvage										
Alexanian et al. [10]	2-2	Chemo 79 SCT 49	Chemo 62 (NS) SCT 62 (52)	NS	Chemo NS SCT 14%	NS	3	NS	NC	NS
Mixed Disease Status—De Novo and Salvage										
Malpas et al. [11]	2-2	Chemo 120 BMT 36	All patients 84 (62) Chemo 84 (NS) SCT 70 (NS)	71%	Chemo 25% BMT 19.5%	Chemo 63.6 BMT NS	I¶	Chemo 20 BMT 72	NC	NS
Gertz et al. [12]	2-1	67	68 (52)	NS	NS	NS	NC	17.2	NC	NS

DS indicates Durie-Salmon; TRM, treatment-related mortality; F/U, follow-up; OS, overall survival; EFS, event-free survival; chemo, standard chemotherapy comparison group; BMT, bone marrow transplantation; NYR, not yet reached; NS, not stated in article; SCT, stem cell transplantation (bone marrow and/or peripheral blood); PBSCT, peripheral blood stem cell transplantation; NC, no comparison given in article.

*Quality of evidence definitions are listed in Table 1; strength of evidence definitions are listed in Table 2; †$P \leq .05$ and $> .01$; ‡$P \leq .01$ and $> .001$; §$P \leq .001$ and $> .0001$; ‖$P \leq .0001$; ¶$P = .002$ from multivariate, not survival analysis.

tional chemotherapy consisting of 18 alternating cycles of VMCP and BVAP (n = 100) in newly diagnosed, previously untreated Durie-Salmon stage II or III MM patients aged younger than 65 years [3]. The BMT conditioning regimen consisted of melphalan (MEL) (140 mg/m^2) and total body irradiation (TBI) given in 4 fractions for a total of 8 Gy without lung shielding. Recombinant interferon alpha (IFNa) was administered in 73% of patients in the chemotherapy group starting at cycle 9 until occurrence of relapse (total duration of IFNa was a median of 12 months), and in 70% of the patients in the BMT group starting after hematologic reconstitution (total duration of IFNa was a median of 11 months). Patients were randomly assigned to 1 treatment arm; 74% of the patients in the BMT group underwent transplantation. Reasons for not proceeding to BMT were as follows: death (n = 5), poor performance status (n = 6), abnormal renal function (n = 5), and insufficient amount of bone marrow (BM) collected (n = 10).

By intent-to-treat, patients in the BMT group had a significantly higher response rate (complete or very good partial response: ≥90% decrease in the serum paraprotein level) of 38% versus 14% in the chemotherapy group ($p < .001$). At a median follow-up measured from the time of randomization of 37 months in the chemotherapy group and 41 months in the BMT group, the BMT group had significantly longer event-free survival (EFS) ($P = .01$) and overall survival (OS) ($P = .03$) (Figure 1). The rate of treatment-related deaths was 5% in the chemotherapy group and 7% in the BMT group. Multivariate analysis of prognostic factors demonstrated that low beta$_2$-microglobulin (B2M) level and BMT group assignment were significantly related to prolonged EFS and only a low level of B2M was significantly related to prolonged OS.

Barlogie et al. performed a phase II study of a planned tandem transplant regimen as part of "total therapy" consisting of vincristine, Adriamycin, and dexamethasone (VAD) for 3 cycles, followed by high-dose cyclophosphamide (Cy) and granulocyte-macrophage colony-stimulating factor (GM-CSF), peripheral blood stem cell (PBSC), and/or BM collection, 1 cycle of etoposide, dexamethasone, cytosine arabinoside, and cisplati-

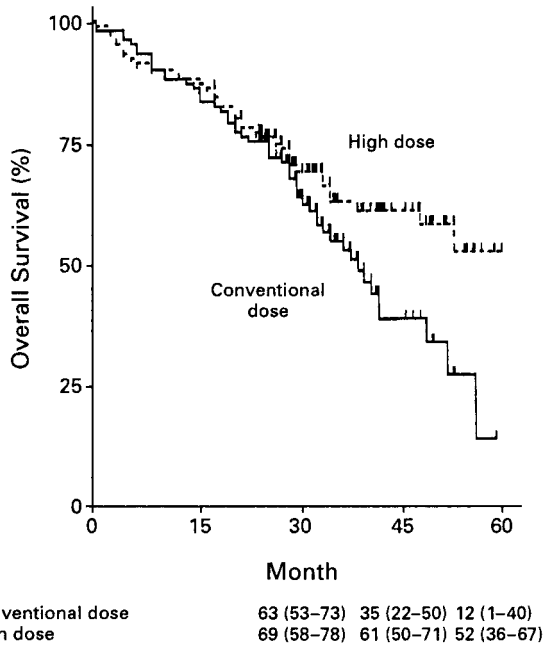

Figure 1. Overall survival according to treatment group. The numbers shown below the time points are probabilities of overall survival (the percentages of patients surviving) and 95% confidence intervals. Reprinted with permission [3].

num (EDAP) [4]. Eligible patients were younger than 70 years of age and had symptomatic MM that was newly diagnosed and previously untreated. The first autologous PBSCT ± BMT conditioning regimen consisted of MEL 200 mg/m^2 and the second autologous PBSCT ± BMT conditioning regimen consisted of MEL 200 mg/m^2 if ≥ partial response (PR) after the first transplantation, otherwise MEL 140 mg/m^2 and TBI in 5 to 6 fractions (850-1020 cGy) were used. IFNa maintenance therapy was administered from hematologic recovery until disease relapse. One hundred and twenty-three patients were initially treated with induction therapy; 87% underwent 1 transplantation and 76% underwent both transplantations a median of 4.5 months apart. Reasons for not undergoing 1 or both transplantations were progression of disease, toxicity of prior therapy, or patient refusal.

For comparison, a sample of historical patients enrolled in Southwest Oncology Group (SWOG) trials 8229 (alternating versus syncopated regimen of VMCP/BVAP) and 8624 (VMCP/BVAP versus VMCPP/BVAPP versus VAD) were pair-matched to the tandem transplant patients based on age, B2M, and serum creatinine levels. By intent-to-treat, patients enrolled in the tandem transplant trial had a significantly higher response rate (≥ PR) than the pair-matched SWOG trial patients (86% versus 52%; P = .0001), longer median duration of EFS (49 versus 22 months; P = .0001), and longer median duration of OS (62+ versus 48 months; P = .01) (Figure 2).

Lenhoff et al. compared 348 symptomatic, newly diagnosed, previously untreated MM patients aged younger than 60 years treated with high-dose therapy from a prospective population-based study (274 of whom were treated according to a Nordic Myeloma Study Group protocol NMSG #5/94) with 313 historical controls aged younger than 60 years selected from 5 previous population-based Nordic studies of conventional therapy (274 of whom fulfilled the eligibility criteria for the NMSG #5/94 protocol and served as the control group) [5]. The authors estimated, based on population-based incidence studies and cancer statistics, that 450 total patients would have been expected in the prospective high-dose therapy study and 410 total patients were expected in the historical control group. Therefore, 61% of the expected incidence of MM patients in the Nordic population were included in the prospective study, and 67% were included in the control group.

NMSG #5/94 consisted of VAD x 3 cycles, PBSC collection after mobilization with Cy and granulocyte colony-stimulating factor (G-CSF), PBSCT with MEL 200 mg/m^2 as conditioning, and maintenance IFNa starting 2 months after engraftment until occurrence of relapse. Autologous PBSCT was completed in 78% of patients; reasons for not performing autologous PBSCT were as follows: allogeneic SCT (n = 4), syngeneic SCT (n = 1), early death (n = 12), progressive disease (n = 11), < PR

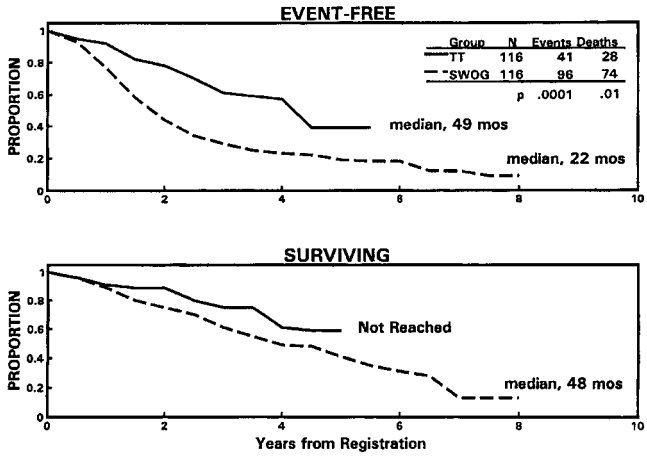

Figure 2. Superior EFS (top) and OS (bottom) among 116 newly diagnosed patients receiving "total therapy" (TT) compared with 116 closely matched "pair mates" receiving standard therapy according to SWOG protocols. The median times of follow-up of living patients on TT and SWOG studies are 31 and 63 months, respectively. Reprinted with permission [4].

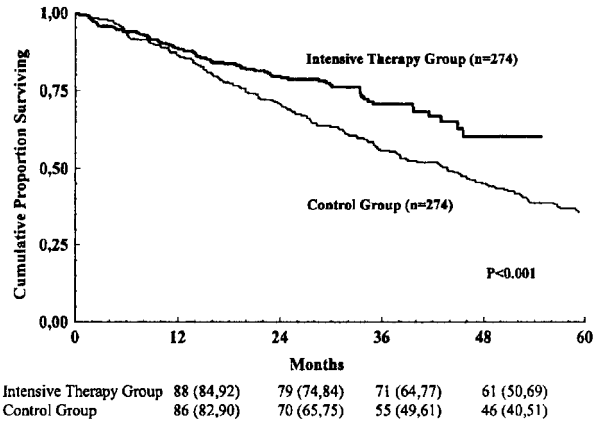

Figure 3. Survival for the intensive therapy group and the control group. The numbers shown below the time points are probabilities of survival in percent, with 95% confidence intervals in brackets. Reprinted with permission [5].

after induction with VAD x 3 cycles (n = 12), contraindications to high-dose chemotherapy (n = 16), and patient refusal (n = 4). The control group consisted of patients from 2 randomized studies of melphalan plus prednisone (MP) versus MP plus IFNa and 3 observational incidence studies.

By intent-to-treat, OS was significantly longer for the PBSCT group compared with the historical control group (median OS: PBSCT not yet reached, control 44 months; risk ratio for controls 1.62; 95% confidence interval [CI] 1.22-2.15; P = .001). After adjustment for differences between the 2 groups with respect to serum creatinine levels, BM plasma cells, serum calcium, and serum hemoglobin, the survival advantage persisted. Age, sex, Durie-Salmon stage, M-protein class, osteolytic bone lesions, serum albumin levels, and platelet count were not significantly associated with OS. Information on performance status and B2M was available for less than half of controls; therefore, the effect of these variables on OS was not evaluated (Figure 3).

Palumbo et al. treated 71 elderly MM patients (aged 55 to 75 years) with 2 to 3 cycles of MEL (100 mg/m^2) each followed by PBSC infusion (treated 1993 to 1997) [6]. Patients who underwent PBSCT were compared with a sample of 71 patients (treated 1990 to 1995) matched by age and B2M chosen from a cohort of symptomatic MM patients treated at diagnosis with oral MP and who met eligibility criteria for the PBSCT regimen. Induction therapy in the PBSCT group consisted of VAD for 2 to 3 cycles followed by Cy plus G-CSF for mobilization; all PBSC collections occurred before the first course of MEL. By intent-to-treat, OS and EFS were significantly longer for the PBSCT group. There were no toxic deaths in the PBSCT group versus 4% in the MP group.

Alexanian et al. compared 68 MM patients who received autologous BMT or PBSCT within 1 year after the start of induction chemotherapy with responsive disease (PR or complete response [CR] to induction) with 50 concurrent control patients with similar disease characteristics and prognostic factors [7,8]. Control patients were responsive to the same therapies as the group that underwent transplantation and met the eligibility criteria for intensive therapy but did not receive this treatment due to patient refusal or denied insurance coverage. For the SCT group, induction therapy consisted of VAD for ≥2 cycles (n = 12), pulse dexamethasone (n = 30), high-dose Cy plus Etoposide plus pulse dexamethasone (n = 18) or a combination of fractionated high-dose Cy with VAD (n = 8). Conditioning regimens were MEL (140 mg/m^2) plus TBI (850 cGy) (n = 21), thiotepa, busulfan, and Cy (n = 40) or thiotepa, busulfan, Cy, and cyclosporine (n = 7). Treatment-related deaths occurred in 7% of patients who underwent SCT. The median OS of patients who underwent SCT was 10 months longer than that of controls (P = .12). Median OS of patients who converted from PR to CR after SCT was significantly longer (8.3 years) than those who remained in PR after SCT (5.0 years) and the controls with persistent PR after standard therapy (4.4 years) (P = .03).

Gianni et al. compared 19 historical controls treated according to a multicenter randomized study of MEL plus prednisone or alternating cycles of VMCP/BVAP with 13 patients treated with a high-dose sequential (HDS) regimen [9]. This HDS regimen consisted of Cy plus GM-CSF or 1 to 2 cycles of VAD, followed by vincristine/methotrexate/etoposide, GM-CSF, leukapheresis +/- BM harvest, and autologous PBSCT (n = 10) or PBSC plus BMT (n = 3) with melphalan (120 mg/m^2) plus TBI (1000 cGy) as the conditioning regimen. Twelve (92%) patients completed the HDS regimen. Both median freedom from progression (FFP) and median OS were significantly longer in the patients who were treated with the HDS regimen compared with the historical chemotherapy-treated controls (FFP: 38 versus 7 months, P = .0003; OS: 41 versus 14 months, P = .0028).

Salvage

Alexanian et al. studied 49 MM patients who received VAD plus autologous BMT or PBSCT compared with 79 contemporaneous controls who received VAD but did not meet the eligibility criteria for myeloablative therapy due to patient refusal, denial of insurance coverage, or ineligibility for TBI due to prior spinal radiotherapy [10]. All patients had been treated with at least 1 year of therapy prior to VAD or VAD plus transplantation. Patients who underwent transplantation and controls were divided into 3 disease response groups: resistant relapse (relapsing despite VAD), primary resistance (resistant to primary therapy for at least 1year), and late remission (in remission after VAD for treatment of resistant disease). The transplant conditioning regimen consisted of either MEL (140 mg/m^2) plus TBI (850 cGy) (n = 26), thiotepa (750 mg/m^2) plus busulfan (10 mg/kg) plus Cy (120 mg/kg) (n = 18), or thiotepa plus TBI (n = 5). In each disease response group, there was no significant difference between the VAD plus transplantation versus the VAD patients with respect to OS or disease-free survival (DFS).

Mixed Disease Stage (De Novo and Salvage)

Malpas et al. retrospectively compared a cohort of 156 patients treated with conventional chemotherapy or autologous BMT [11]. The article does not state the median number of chemotherapy regimens in either patient group. Thus the proportion of patients transplanted as de novo versus salvage therapy is undetermined. One hundred and twenty patients received MEL (140 mg/m^2), MP, or Cy as conventional chemotherapy. Thirty-six autologous BMT patients received a single agent conditioning regimen with either MEL (220 mg/m^2) or busulfan (4 mg/kg/d x 4 days). Eleven (31%) of the BMT patients and

Table 6. *Comparison of Patient Characteristics and Outcomes from Articles Included in Timing of Transplant (De Novo versus Salvage) Section*

Reference	Quality of Evidence*	Number of Patients in Study	Upper Age Limit (Median)	DS Stage III	TRM	Median F/U (mos)	Strength of Evidence—OS*	Median OS (mos)	Strength of Evidence—EFS*	Median EFS (mos)
Fermand et al. [13]	1	Early 91 Late 94	Early 56 (48 mean) Late 56 (47 mean)	Early 87% Late 82%	Early 10% Late 14%	58	3	Early NYR (64.6+) Late NYR (64+)	1†	Early 39 Late 13
Harousseau et al. [14]	2-1	De novo 53 Salvage 44	De novo 67 (51) Salvage 67 (51)	De novo 94% Salvage 84%	De novo 4% Salvage 10%	32	3	NS	NC	NS
Hawkins et al. [15]	2-2	29	63 (56)	63%	17%	28	3	De novo 47‡ Salvage 71	NC	NS
Alegre et al. [16]	2-2	259	67 (52)	69%	4%	13	1§	De novo 45 Salvage 28	NC	NS

DS indicates Durie-Salmon; TRM, treatment-related mortality; F/U, follow-up; OS, overall survival; EFS, event-free survival; NYR, not yet reached; NS, not stated in article; NC, no comparison given in article.

*Quality of evidence definitions are listed in Table 1; strength of evidence definitions are listed in Table 2; †$P < .001$ (calculated by authors, P not stated in article). ‡OS from diagnosis; §$P \leq .05$ and $> .01$.

none of the conventional chemotherapy patients received IFNa maintenance therapy. OS in the BMT group was prolonged (median 6 years) compared to the conventional chemotherapy group (median 20 months, P value not stated in original manuscript). Multivariate analysis showed increasing age ($P = .05$) and treatment with conventional chemotherapy ($P = .002$) were independent risk factors for shorter OS.

Gertz et al. also reported on 118 MM patients who had VAD x 4 cycles as either induction or re-induction (after prior MEL-based chemotherapy) therapy and G-CSF (n = 46), G-CSF plus Cy (n = 58), or non-mobilized (n = 14) PBSCs collected and cryopreserved within 6 months of diagnosis [12]. Patients who had primary treatment failure went on to PBSCT (n = 11); all others were treated with vincristine, BCNU, MEL, cyclophosphamide, and prednisone (VBMCP) maintenance therapy for 12 cycles and underwent transplantation at first sign of disease progression. A total of 67 patients underwent transplantation (11 early treatment failures and 56 as a result of progression on or off maintenance therapy) with a median OS after PBSCT of 17.2 months. Median OS from initial MM diagnosis of all 118 transplantation and non-transplantation patients was 58.5 months. There was no comparison of PBSCT as de novo versus salvage therapy.

TIMING OF TRANSPLANTATION (DE NOVO VERSUS SALVAGE)

Table 6 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcome measures for the articles detailed in this section. Fermand et al. performed a multicenter prospective randomized trial comparing the optimal timing of autologous PBSCT [13]. After enrollment, all patients received 1 to 2 cycles of intensified CHOP (cyclophosphamide 1500 mg/m^2, Adriamycin 90 mg/m^2, vincristine 1.4 mg/m^2, and prednisone; the second cycle also included G-CSF) followed by PBSC collection then randomization to early versus late PBSCT. The early transplantation group (n = 91) received 3 to 4 cycles of vincristine, adriamycin, and methylprednisolone (VAMP) followed by autologous PBSCT with lomustine (120 mg/m^2 day -8), etoposide (250 mg/m^2 days -8 to -6), Cy (60 mg/kg day -5), MEL (140 mg/m^2 day -4) and TBI (1200 cGy in 6 fractions days -3 to -1). Patients in the late transplantation group (n = 94) received VMCP as induction therapy until a stable plateau phase was reached. Once patients showed either disease progression while receiving VMCP, disease resistance (no response or <PR after 6 courses of VMCP), or relapse after responding (n = 81), they then received monthly VAMP followed by autologous PBSCT as rescue therapy. IFNa was used in 56% of remission patients in the early transplantation group and 60% of remission patients in the late transplantation group. At a median follow-up of 58 months, there was no significant difference in OS, however, there was a significant difference in EFS; the early transplantation group's median was 39 months (95% CI, 29 to 48) versus the late transplantation group's median of 13 months (95% CI, 9.4 to 17.6). The median time without symptoms, treatment, or treatment toxicity (TWiSTT) was 27.8 months (95% CI, 23.8 to 31.8) for the early transplantation group and 22.3 months (95% CI, 16.0 to 28.6) for the late transplantation group (Figure 4).

Harousseau et al. treated 97 MM patients with one course of high-dose MEL (120-140 mg/m^2) without stem cell rescue [14]. Before this first course of high-dose MEL, patients were divided into 2 groups for analysis: group 1 included 14 primary refractory and 30 relapsed patients (salvage), group 2 included 53 newly diagnosed untreated patients (de novo). Thirty-five patients who achieved a PR or CR to the first course of high-dose MEL (10 from group 1 and 25 from group 2) received an autologous BMT (n = 31) or PBSCT (n = 4). Conditioning regimens were MEL (140 mg/m^2; n = 18), MEL (140 mg/m^2) plus TBI (1000-1200 cGy) or Cy plus TBI (1000-1200 cGy) (n = 16 for combined MEL plus TBI and Cy plus TBI groups) or BuCy (n = 1). Considering all 97 patients, those in group 2 treated as de novo had a longer median OS from first course of high-dose MEL compared with those in group 1 given high-dose MEL plus SCT as salvage therapy (37 versus 17 months; $P = .16$). In the 35 patients who received autologous SCT, there

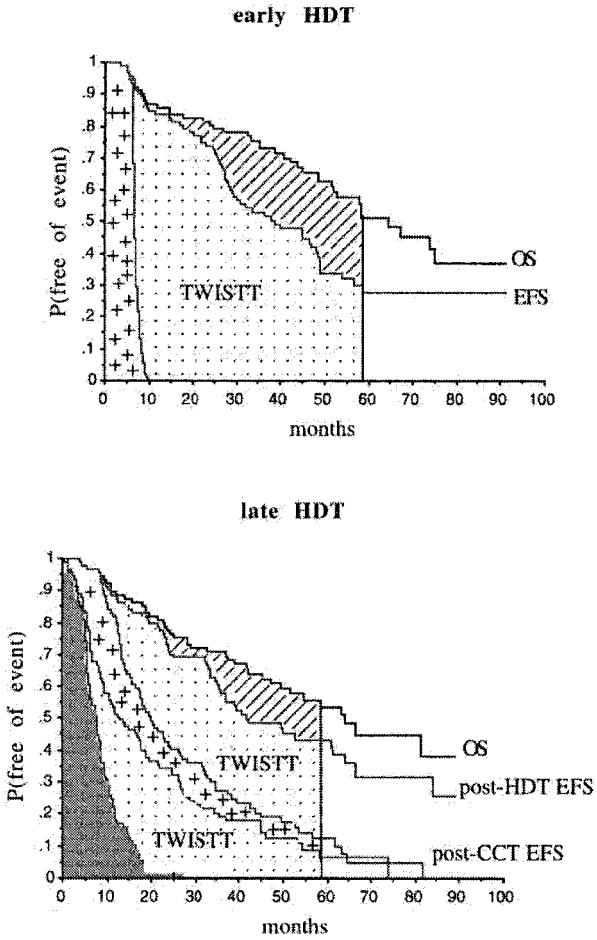

Figure 4. Partitioned Kaplan-Meier survival curves according to treatment group, ie, early HDT group (top) and late HDT group (bottom). Each plot displays the Kaplan-Meier estimations of time to OS, EFS, and time to end of treatment, either conventional chemotherapy (CCT) or transplantation (HDT), since randomization. Note that 2 EFS were considered in the late HDT group (after conventional chemotherapy, "post-CCT," and after transplantation, "post-HDT"). The areas between these curves and the vertical line at 58 months, which corresponds to the median follow-up of the whole cohort, represent estimates of the mean durations between these events, namely treatment duration (either CCT [▨] or HDT [+]), time without symptoms and treatment toxicity (TWISTT [▩]), and time between relapse and death (▨). All patients were included in the analysis on an intent-to-treat basis. IFN was not taken into account because it was usually maintained only when well-tolerated. Reprinted with permission [13].

was no significant difference in OS or progression-free survival (PFS).

Hawkins et al. reported on 29 MM patients treated with autologous PBSCT as de novo (n = 13) or salvage (n = 16) therapy [15]. Median number of prior chemotherapy cycles before PBSCT was 7 (range, 0-21). Sixteen patients were responsive (≥PR) and 13 were resistant (<PR) to debulking chemotherapy given pre-SCT. De novo patients had a significantly lower treatment-related mortality (TRM) (6% versus 32%; P = .027), higher CR rate (46% versus 9%; P = .047), and longer median OS post-PBSCT (33 versus 15 months; P = .01) compared with previously treated patients.

Alegre et al. reported on 259 MM patients from the Spanish Registry (GETH and PETHEMA) treated with autologous PBSCT [16]. Conditioning regimens consisted of MEL (n = 96), MEL plus TBI (n = 73), MEL plus busulfan (n = 56), busulfan plus Cy (n = 27), and Cy plus TBI (n = 7). At the time of transplantation, patients were in CR (n = 56), PR (n = 153), no response (n = 25), or progressive disease (n = 25). Fifty-two percent of patients had only one prior chemotherapy regimen (de novo); 48% had 2 or more prior chemotherapy regimens (salvage). Multivariate analysis showed the only independent factors associated with OS and PFS were number of chemotherapy regimens (1 versus other) prior to autologous PBSCT and the disease status prior to PBSCT (CR/PR versus other).

AUTOLOGOUS VERSUS ALLOGENEIC SCT

Table 7 summarizes the grading evaluation of the quality and strength of the evidence, patient characteristics, and outcomes of the articles reviewed in this section. Lokhorst et al. prospectively treated 77 newly diagnosed de novo MM patients with VAD x 2 plus intermediate-dose MEL (IDM) (70 mg/m^2) for 2 cycles (n = 62) or IDM for 2 cycles (n = 15) as induction

Table 7. *Comparison of Patient Characteristics and Outcomes from Articles Included in Autologous versus Allogeneic SCT Section*

Reference	Quality of Evidence*	Number of Patients in Study	Upper Age Limit (Median)	DS Stage III	TRM	Median F/U (mos)	Strength of Evidence—OS*	Median OS (mos)	Strength of Evidence—EFS*	Median EFS (mos)
Lokhorst et al. [17]	2-1	77	Auto 63 (53) Allo 55 (43)	81% (all patients)	Auto 4% Allo 18%	44 (all patients)	3	Auto NYR Allo NYR	2	Auto 40 Allo NYR
Seiden et al. [18]	2-1	Auto 36 Allo 22	Auto 65 (48) Allo 56 (44)	66% (all patients)	Auto 3% Allo 9%	Auto 27 Allo 20	NC	Auto NYR Allo NS	NC	NS
Bjorkstrand et al. [21]	2-2	Auto 189 Allo 189	Auto 65 (49) Allo 60 (43)	Auto 67% Allo 65%	Auto 13% Allo 41%[a]	Auto 30 Allo 46	1[†]	Auto 34 Allo 18	NC	NS
Varterasian et al. [22]	2-2	Auto 24 Allo 24	Auto 64 (55) Allo 56 (43)	Auto 21% Allo 18%	Auto 12.5% Allo 25%	Auto 11 Allo 15	3	Auto 33.5 Allo 38.6	3	Auto 16.7 Allo 31
Reynolds et al. [23]	2-2	Auto 35 Allo 21	Auto 68 (55) Allo 56 (48)[‡]	NS	Auto 6% Allo 19%	Auto 15.4 Allo 27.5[‖]	3	Auto NYR Allo NYR	NC	NS
Couban et al. [24]	2-2	Auto 40 Allo 22	Auto 57 (45.5) Allo 53 (43)	Auto 62% Allo 50%	Auto 5% Allo 27%	Auto 15 Allo 42	1[§]	Auto NYR (48+) Allo 7	NC	NS

DS indicates Durie-Salmon; TRM, treatment-related mortality; F/U, follow-up; OS, overall survival; EFS, event-free survival; auto, autologous SCT; allo, allogeneic SCT; NYR, not yet reached; NC, no comparison given.

*Quality of evidence definitions are listed in Table 1; strength of evidence definitions are listed in Table 2; [†]$P \leq .001$ and $>.0001$; [‡]$P \leq .01$ and $> .001$; [§]$P \leq .05$ and $> .01$.

therapy [17]. Patients with at least a PR to induction therapy and an adequate stem cell harvest and who were aged younger than 65 years received autologous PBSCT followed by IFNa maintenance (n = 50). Those who had at least a PR to induction therapy, a human leukocyte antigen (HLA)-identical sibling donor, and were younger than 56 years received an allogeneic BMT (n = 11). The conditioning regimen consisted of Cy plus TBI for both groups; however autologous PBSCT patients received 9 Gy (8 Gy lung dose) in a single dose whereas allogeneic BMT patients received 12 Gy (8.5 Gy lung dose) in 2 fractions. Allogeneic BMT patients received a T-cell depleted graft and cyclosporin A for graft-versus-host disease (GVHD) prophylaxis.

Twenty-two percent of patients did not undergo SCT due to disease progression or no response to induction (n = 12), inadequate stem cell (SC) harvest (n = 3), or poor performance status (n = 1). B2M, lactate dehydrogenase (LDH), Durie-Salmon stage, and performance status were not significantly different between the autologous, allogeneic, and no SCT groups. There was no statistically significant difference in OS between the autologous and allogeneic transplantation groups (median OS not yet reached in either group), however, there was a trend toward improved EFS in the allogeneic BMT group ($P = .078$).

Seiden et al. performed a prospective study in MM patients (including 2 with plasmacytomas) of autologous monoclonal antibody purged BMT (n = 36) or a T-cell depleted allogeneic BMT (n = 21, including 1 syngeneic BMT) if an HLA-compatible sibling donor was available [18-20]. All patients had received a median of 3 prior regimens and were in sensitive relapse (<10% plasma cells in BM) at the time of BMT as salvage therapy. Conditioning regimens for autologous BMT patients were MEL (140 mg/m^2) plus TBI (1200 cGy; n = 20) or Cy plus TBI (1200-1400 cGy; n = 16). Conditioning regimens for allogeneic BMT patients were Cy plus TBI (1400 cGy; n = 19 allografts and 1 syngeneic) or busulfan plus Cy (n = 2). Eighty-one percent of autologous BMT patients were alive at the median follow-up of 27 months versus 64% of allogeneic BMT patients alive at a median follow-up of 20 months. Thirty-nine percent of autologous patients were alive and FFP 18 months post-BMT versus 33% of allogeneic patients alive and FFP 30 months post-BMT.

Bjorkstrand et al. retrospectively compared 189 allogeneic BMT patients with HLA-identical sibling donors to 189 autologous PBSCT patients in a matched case control study using European Group for Blood and Marrow Transplantation (EBMT) Registry data [21]. Patients were matched on gender and number of previous chemotherapy regimens. Conditioning regimens for autologous PBSCT were MEL plus TBI (n = 62), MEL (n = 35), MEL plus Cy plus TBI (n = 20), MEL plus other drug combinations (n = 39), Cy plus TBI (n = 10), etoposide plus TBI (n = 9), busulfan plus Cy (n = 9), or other drug combinations (n = 5). Conditioning regimens for allogeneic BMT were Cy plus TBI (n = 83), busulfan plus Cy (n = 35), MEL plus Cy plus TBI (n = 34), Cy plus TBI with MEL and/or other drugs (n = 23), TBI plus drug combinations not including MEL or Cy (n = 9), or busulfan plus Cy plus other drugs (n = 5). Median OS was significantly longer in the autologous PBSCT group compared with the allogeneic BMT group (34 versus 18 months; $P = .001$), however, after stratification by gender, this survival advantage was observed in men only and not in women. The survival advantage persisted after correcting for significant differences in the median follow-up times post-transplantation by selecting 174 allogeneic BMT patients with their contemporaneous matched autologous PBSCT controls. Median PFS also was longer in the autologous PBSCT group (18 versus 10 months), however, at 24 months after transplantation, the PFS curves cross and the statistical significance tests could not be calculated.

Varterasian et al. performed a retrospective multicenter comparison of autologous unpurged PBSCT (n = 24) and allogeneic BMT from an HLA-compatible sibling donor (n = 24) in MM patients [22]. The median disease duration for all patients was 28 months during which all patients had received prior

therapy with conventional MM regimens with varied disease responses. Conditioning regimens for autologous PBSCT patients were MEL (140 mg/m^2) plus TBI (n = 23) or MEL (200 mg/m^2) (n = 1) and 1 of the following 4 combinations for allogeneic BMT patients: Cy plus TBI (1200 cGy) (n = 15), busulfan plus Cy plus total marrow irradiation (TMI) (n = 5), cyclophosphamide, etoposide, BCNU (CVB) (n = 3), or MEL (140 mg/m^2) plus TBI (n = 1). At a median follow-up of 11 months for the autologous and 15 months for the allogeneic transplantation patients, there was no significant difference in median OS (33.5 versus 38.6 months; $P = .7637$) or median EFS (16.7 versus 31 months; $P = .8450$).

Reynolds et al. performed a retrospective single center comparison of 35 autologous PBSCT patients with 21 historical allogeneic BMT (n = 6) or PBSCT (n = 15) patients with HLA-identical (n = 20) or 1 antigen mismatched (n = 1) related donors; both autologous and allogeneic SCT patients were given an identical conditioning regimen: busulfan plus Cy plus TBI (900 cGy) [23]. Before SCT, patients were treated with at least 1 cytoreductive regimen until best response; median time from diagnosis to SCT was 238 days in the autologous group and 276 days in the allogeneic group ($P = .75$). The Kaplan-Meier probability of disease progression was 11% in the allogeneic group and 64% in the autologous group ($p < .001$). Two-year PFS (60% versus 30%; $P = .19$) and 2-year OS (60% versus 42%; $P = .39$) were higher in the allogeneic group but were not statistically significantly different. TRM was higher in the allogeneic group but not significantly different than the autologous group.

Couban et al. retrospectively compared a cohort of 40 autologous PBSCT and 24 allogeneic (including 2 syngeneic) BMT or PBSCT patients transplanted for MM at a single center [24]. All allogeneic transplant recipients had related HLA-matched (6/6) donors. All patients had 1 to 4 chemotherapy regimens before transplantation and underwent transplantation as de novo or salvage therapy. Patients treated with autologous versus allogeneic transplants had comparable disease status at time of transplantation. Conditioning regimens for autologous transplants were MEL (160 mg/m^2), TBI (1200 cGy), and etoposide (n = 29), busulfan plus Cy (n = 8), or MEL (160 mg/m^2) plus TBI (500 cGy in a single fraction) (n = 3). Conditioning regimens for allogeneic transplants were Cy plus TBI (1200 cGy) (n = 14), busulfan plus Cy (n = 9), or MEL (160 mg/m^2) plus TBI (1200 cGy in 6 fractions) (n = 1). Three-year PFS was not statistically significantly different between autologous (17%; 95% CI, 0-36.6) and allogeneic (22%; 95% CI, 4-39.6) transplants. Three-year OS was significantly higher in autologous (74%; 95% CI, 52.4-95.6) versus allogeneic (32%; 95% CI, 12.4-51.6) transplant patients.

AUTOLOGOUS SCT

Several studies have demonstrated the feasibility, safety, and efficacy of PBSCT and/or BMT with MEL-based conditioning regimens in previously untreated, newly diagnosed MM patients [25-28], as salvage therapy for relapsed or refractory disease [29-35], and in MM patient populations with mixed disease responses to prior therapy [36-41]. Three studies demonstrated the safety and efficacy of autologous transplantation: 1 study in 17 MM patients aged older than 65 years [42], 1 study in 70 patients aged 70 years or older [43], and 1 study in 10 patients with active ongoing respiratory syncytial virus (RSV) infection [44], and 4 studies have been completed for patients in renal failure (total 99 patients, 48 of whom were on chronic hemodialysis) [45-48].

Autologous Peripheral Blood versus BMT

Raje et al. compared two sequential phase II studies: the first of patients receiving autologous BMT (n = 26), the second of individuals treated with autologous PBSCT (n = 37) [49]. Median age was 50 years for BMT patients and 49 years for PBSCT patients. Seventy-three percent of BMT and 76% of PBSCT patients had stage III disease. All patients received induction therapy with Cy, vincristine, adriamycin, and methylprednisolone (C-VAMP), conditioning regimen of MEL (200 mg/m^2), and IFNa maintenance therapy posttransplantation. PBSCs were mobilized with G-CSF alone. Median follow-up of both groups was 30 months. The two groups showed no significant differences in known prognostic factors, including age, gender, disease stage, performance status, serum creatinine level, or B2M. PBSCT patients recovered platelets significantly faster than BMT patients (19 versus 33 days; $P = .0015$), however, there were no significant differences between the groups with regard to neutrophil engraftment, OS, or PFS.

Harousseau et al. retrospectively compared 81 autologous BMT patients with 51 autologous PBSCT patients from 18 French centers who were treated during a 7-year period [50]. The median ages were 55 years for BMT and 49 years for PBSCT patients. Stage III disease was present in 86% of BMT and 80% of PBSCT patients. Significant differences between the 2 patient groups were found for age (PBSCT 49 years versus BMT 55 years, $P < .001$), duration of prior chemotherapy, interval between stem cell collection and transplantation, and conditioning regimen (more TBI-containing regimens and higher doses of irradiation in the PBSCT group). Overall median follow-up was 35 months. There was no significant difference between the PBSCT and BMT groups regarding CR rate, overall response rate, OS, EFS, or relapse-free survival (RFS). A subgroup analysis matching 43 PBSCT and 43 BMT patients for age and disease status at time of transplantation also showed no significant difference between the two groups regarding median OS (BMT 31 versus PBSCT 45 months), median EFS (BMT 18 versus PBSCT 22 months), or median RFS (BMT 33 versus PBSCT 36 months). PBSCT patients had a significantly shorter time to neutrophil engraftment but no significant difference in platelet recovery compared with BMT patients.

Autologous CD34+ Selected versus Unselected PBSCT

Table 8 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcomes of the articles reviewed in this section.

Stewart et al. performed a multicenter randomized phase III trial of CD34+ selected (n = 93) versus unselected PBSCT (n = 97) for the treatment of MM [51,52]. Although CD34+ selection significantly reduced the tumor burden in the stem cell products measured as the identification of a clonal immunoglobulin (Ig) sequence by a median of 3.1 logs [51], there was no difference in the median PFS (100 versus 104 weeks; $P = .82$) (Figure 5) or median OS (202 weeks versus not yet reached; $P = .784$) between the CD34+ selected versus unselected treatment arms [52]. There also was no significant difference in the median

Table 8. *Comparison of Patient Characteristics and Outcomes from Articles Included in the Autologous CD34+ Selected versus Unselected PBSCT Section*

Reference	Quality of Evidence	Number of Patients in Study	Upper Age Limit (median)	D-S Stage III	TRM	Median Follow-Up (mos)	Strength of Evidence*	Median d to ANC > 500/mm^3	Strength of Evidence†	Median d to Platelets > 20,000/mm^3
Stewart et al. [51]	1	Sel 93 Unsel 97	Sel 70 (51) Unsel 68 (53)	NS	NS	37	3	NS	3	NS
Abonour et al. [53]	2-1	18	65 (53)	44%	NS	25	NC	11	NC	15
Lemoli et al. [54]	2-1	23	55 (47.5)	59%	NS	12	3	Sel 10 Unsel 10	3	Sel 11 Unsel 15
Schiller et al. [57]	2-1	55	69 (52)	55%	11%	33	NC	12	NC	12
Dyson et al. [59]	2-1	34	65 (51)	NS	NS	NS	NC	NS	NC	NS
Patriarca et al. [60]	2-1	Sel 23 Unsel 16	Sel 63 (54) Unsel 62 (55)	Sel 65% Unsel 63%	NS	18	3	Sel 12 Unsel 12	3	Sel 21 Unsel 16
Gupta et al. [61]	2-1	Sel 20 Unsel 16	Sel 62 (NS) Unsel 64 (NS)	NS	0%	23	3	Sel 14 Unsel 14	3	Sel 14 Unsel 13
Michallet et al. [62]	2-1	23	65 (55)	77%	9%	15	1	Higher Dose‡ 10 Lower Dose‡ 12	1	Higher Dose 13 Lower Dose 64
Lemoli et al. [63]	2-1	Single 35 Tandem 47	Single 64 (51) Tandem 60 (52)	Single 69% Tandem 66%	4%	Single 34 Tandem 28	Single 3 Tandem 3	NC	Single 3 Tandem 3	NC
Gandhi et al. [64]	2-2	Sel 15 Unsel 15	Sel 64 (53) Unsel 63 (55)	Sel 67% Unsel 60%	Sel 13% Unsel 7%	Sel 32 Unsel 57	1§	Sel 14 Unsel 11	1§	Sel 23 Unsel 14

DS indicates Durie-Salmon Stage; TRM, treatment-related mortality; ANC, absolute neutrophil count; NS, not stated in original article; NC, not compared in original article; Sel: CD34+ Selected, Unsel: CD34+ Unselected.

*Strength of evidence comparing neutrophil engraftment; †strength of evidence comparing platelet engraftment; ‡higher dose: CD34+Thy1+ $>0.8 \times 10^6$ cells/kg, lower dose: CD34+Thy1+ $<0.8 \times 10^6$ cells/kg. §, $P \leq .05$ and $> .01$.

time to neutrophil engraftment between the CD34+ selected versus unselected groups. There was a trend toward a significantly slower platelet recovery in the selected arm (at day 100, 15% versus 26% had platelet recovery; $P = .052$).

Several feasibility studies of CD34+ selection of PBSC harvests previously had demonstrated its ability to reduce the tumor burden in the products without adversely affecting engraftment kinetics [53-58]. One study demonstrated the feasibility of performing CD34+ selection on the products from multiple cycles of stem cell mobilization and collection [59].

Two studies compared CD34+ selected versus unselected autologous PBSCT patients in prospective, non-randomized clinical trials and found no significant differences in neutrophil or platelet recovery between the 2 groups [60,61]. One study

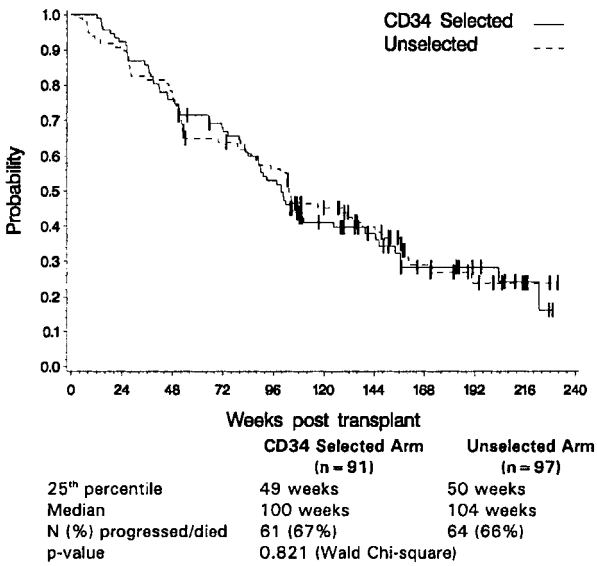

Figure 5. Kaplan-Meier probability of progression-free survival of 188 patients on an intent-to-treat basis. Reprinted with permission [51].

demonstrated that all patients who received a high cell dose of $>0.8 \times 10^6$ CD34+Thy1+ cells/kg had significantly faster neutrophil engraftment (median 10 days versus 12 days; $P = .003$) and platelet recovery (median 13 days versus 64 days; $P = .008$) than those who received a low cell dose of $<0.8 \times 10^6$ CD34+Thy1+ cells/kg [62].

One study compared single versus tandem CD34+ selected PBSCT in a non-randomized prospective trial [63]. There was no difference in platelet or neutrophil recovery in single or tandem SCT when comparing CD34+ selected versus unselected PBSCT. One case-control study showed a significantly longer time to neutrophil and platelet recoveries in CD34+ selected PBSCT patients but no difference in PFS or OS [64].

Autologous Purged versus Unpurged SCT

Reece et al. reported the feasibility of BMT in 14 patients with marrow purged ex vivo with 4-hydroperoxycyclophosphamide [65]. Forty-three patients underwent evaluation at diagnosis of MM, 24 of whom received VAD for induction therapy. Seventeen patients were eligible for BMT based on adequate disease response, 16 of whom underwent harvesting. Two patients who underwent harvesting showed high (>40%) percentages of plasma cells in their harvests, leaving 14 patients with a median of 3% plasma cells (range, 1%-7%) before purging who underwent transplantation with purged BM. All patients achieved neutrophil engraftment a median 19 days post-BMT and the last platelet transfusion was given a median 32 days post-BMT. Four of the 14 BMT patients were alive and progression-free a median 20 months after BMT.

Lemoli et al. described the feasibility of PBSCT with CD34+ selected products followed by negative selection using ex vivo immunomagnetic depletion to purge CD10+, CD19+, CD20+, and CD56+ (B-lin) cells [66]. Fourteen patients were mobilized with Cy plus G-CSF, 2 of whom did not mobilize adequate CD34+ cells and were infused with unmanipulated PBSC. Therefore, 12 patients underwent transplantation with CD34+ B-lin- cells after conditioning with MEL (200 mg/m^2). Median time from diagnosis to PBSCT was 45 months (range, 5 to 144 months). All patients engrafted neutrophils a median 12 days (range, 6 to 24 days) and platelets a median 14 days (range, 11 to 25 days) post-PBSCT. At a median follow-up of 14 months, 11 patients were alive, 4 of whom were in continuous CR and 3 had stable disease.

Rasmussen et al. studied the feasibility of PBSCT with CD34+ selected products followed by CD19 depletion in 14 previously untreated MM patients [67]. All patients received VAD x 3 cycles, G-CSF or Cy (4 g/m^2) plus G-CSF, leukapheresis, ex vivo manipulation (CD34+ selection followed by CD19 depletion with murine antibody), and PBSCT with MEL (200 mg/m^2) conditioning. All patients engrafted neutrophils at a median of 11 days (range, 10 to 17 days) and platelets at a median of 12 days (range, 11 to 18 days) post-PBSCT. No patient died of TRM within 100 days post-PBSCT. At a median follow-up of 26 months (range, 7 to 35 months), 13 patients were alive, 3 in continuous CR, 9 in PR, and 1 with stable disease.

Barbui et al. randomized 60 newly diagnosed symptomatic MM patients to receive either unmanipulated (n = 31) or purged (n = 29) tandem PBSCT [68]. All patients were previously untreated and received VAD x 3 cycles, Cy (7 g/m^2) plus G-CSF for stem cell mobilization, randomization to purged versus unpurged PBSCT, leukapheresis, first PBSCT with MEL (200 mg/m^2), and 3 to 6 months later a second PBSCT with either MEL (200 mg/m^2) or MEL (140 mg/m^2) plus TBI. Adequate PBSCs were collected to perform two transplantations (target cell dose of $>4 \times 10^6$ CD34+ cells/kg for each PBSCT). Patients randomized to the purged arm had unmanipulated PBSCs stored as back-up. Purging was performed using monoclonal antibodies against CD19, CD56, and CD138.

Eighty-six percent of patients in the purged and 87% in the unpurged treatment arm completed both transplantations. There was no difference in the time to neutrophil or platelet recovery, discharge from hospital, or transfusion requirements between the purged and unpurged PBSCTs. No patients in either group died of TRM. At the time of the first PBSCT, 23% of purged PBSCT patients and 48% of unpurged PBSCT patients were in CR. At a median follow-up of 23 months, the 3-year EFS rate was 72% in the purged and 40% in the unpurged PBSCT group ($P = .05$). The 3-year OS rate was 83% for the purged and 83% for the unpurged PBSCT groups. By multivariate analysis, factors associated with prolonged EFS were B2M <3 mg/L ($P = .04$), purged PBSCT ($P = .03$), and in CR at time of first PBSCT ($P = .006$).

Autologous Tandem versus Single SCT

Table 9 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcomes of the articles reviewed in this section.

Barlogie et al. compared tandem transplantations versus standard chemotherapy without stem cell support, which has been previously detailed in this review [4]. Additional patients were accrued in the tandem transplantation regimen ("total therapy") and follow-up of the original patients was updated [69]. This updated study reported on 231 patients, of whom 88% completed induction therapy, 84% completed the first transplantation, and 71% completed the second. Fourteen patients received their second planned transplantation from an HLA-matched allogeneic donor. By intent-to-treat, 5-year OS and EFS rates were 58% and 42%, respectively. Statistically significant prognostic factors for prolonged OS and EFS by multivariate analysis were the absence of unfavorable cytogenetics (11q breakpoints and/or partial or complete deletions of chromosome 13) and low B2M.

Vesole et al. compared patients with advanced and refractory MM who received MEL (90-100 mg/m^2) with no stem cell rescue (MEL100) (n = 47) versus MEL (140 mg/m^2) plus TBI or thiotepa plus TBI and autologous BMT (MEL140) (n = 21) versus MEL (200 mg/m^2) with autologous BM plus PBSCT as a tandem transplantation (MEL200) (n = 67) [70]. Patients in the MEL200 group had significantly more favorable prognostic factors (lower incidence of elevated LDH and B2M, resistant relapse, and >12 months of prior therapy) than either the MEL100 and MEL140 groups. A multivariate regression analysis of favorable factors for EFS found that low B2M ($P = .0001$), MEL200 ($P = .0001$), primary unresponsive disease ($P = .004$), and age 50 years or younger ($P = .04$) were statistically significant. B2M, MEL200, ≤12 months from diagnosis, and age 50 years or younger were statistically significant predictors of prolonged OS.

Siegel et al. compared tandem transplantation in a sample of 49 patients with advanced stage MM aged 65 years or older to

Table 9. *Comparison of Patient Characteristics and Outcomes from Articles Included in the Autologous Tandem versus Single SCT Section*

Reference	Quality of Evidence*	Number of Patients in Study	Upper Age Limit (Median)	DS Stage III	TRM	Median F/U (mos)	Strength of Evidence—OS*	Median OS (mos)	Strength of Evidence—EFS*	Median EFS (mos)
Barlogie et al. [69]	2-1	Enrolled 231 2 BMTs 165	71 (51)	53%	5%	NS	NC	68	NC	43
Vesole et al. [70]	2-2	MEL100 47 MEL140 21 MEL200 67	NS	NS	MEL100 19% MEL140 24% MEL200 1%	NS	I†	MEL100 7 MEL140 16 MEL200 NYR (43+)	I‡	MEL100 5 MEL140 8 MEL200 21
Siegel et al. [71]	2-2	<65 49 ≥65 49	<65 64 (52) ≥65 76 (67)	<65 49% ≥65 59%	<65 2% ≥65 8%	NS (minimum 18 months)	3	<65 57.6 ≥65 39.6	3	<65 33.6 ≥65 18
Bjorkstrand et al. [72]	2-1	1 BMT 15 2 BMTs 11	57 (48)	73%	7%	21 (after first transplantation)	NC	NYR (19+)	NC	NS

DS indicates Durie-Salmon; TRM, treatment-related mortality; F/U, follow-up; OS, overall survival; EFS, event-free survival; NS, not stated in article; NC, no comparison given in article.

*Quality of evidence definitions are listed in Table 1; strength of evidence definitions are listed in Table 2; †$P = .001$; NYR, not yet reached; ‡$P = .0001$.

pair-mates younger than 65 years matched on 5 prognostic factors (cytogenetics, B2M, C-reactive protein, albumin, and creatinine) [71]. All patients received MEL (200 mg/m^2) as the conditioning regimen for the first transplantation. If ≥PR was achieved/maintained after the first, MEL200 was used again for the second SCT; if <PR was achieved/maintained, then MEL140 plus TBI (850-1125 cGy) or MEL200 plus Cy (6 g/m^2) was given as the preparative regimen. Median durations of EFS and OS and TRM were not significantly different between the younger and older groups. Multivariate analysis identified unfavorable cytogenetics and elevated B2M as significant predictors of poor EFS and OS; age younger than 65 years, however, was not a statistically significant factor for either EFS or OS.

Björkstrand et al. reported on 15 patients with MM intended to have tandem autotransplantations [72]. BM (n = 13) or PBSCs (n = 2) were used for the first transplantation and PBSCs (n = 11) were used for all second transplantations. Conditioning regimen was MEL (200 mg/m^2) for the first transplantation and MEL (140 mg/m^2) plus TBI (1000 cGy) for the second. Four patients did not receive the second transplant due to incomplete hematopoietic reconstitution (n = 3) or TRM (n = 1). Analysis of molecular remission was performed using Ig gene fingerprinting in 5 of 8 patients in CR after the second transplantation. The original clonal band was not detected in 4 of the 5 patients a median 27 months after second transplantation. A new band was detected in 1 patient 32 months after the second transplantation, who 4 months later demonstrated clinical disease progression. At a median 20.7 months after the first transplantation, 8 patients were in continuous CR, 3 in continuous PR, 2 were alive with progressive disease, 1 died of treatment-related toxicity, and 1 died of progressive disease.

Autologous SCT Conditioning Regimens

Table 10 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcomes of the articles reviewed in this section.

Moreau et al. performed a randomized multicenter clinical trial of 142 patients with MM treated with MEL (200 mg/m^2) versus 140 patients treated with MEL (140 mg/m^2) plus TBI (800 cGy) as the conditioning regimen for autologous PBSCT [73]. Eligibility criteria included age younger than 65 years and newly diagnosed, previously untreated, and symptomatic MM. After enrollment, patients received VAD x 3 cycles, stem cell mobilization with G-CSF, G-CSF plus stem cell factor (SCF) or Cy (4 gm/m^2) plus G-CSF, PBSC collections (if no disease progression after VAD), 1 additional VAD cycle, and randomization to 1 of the conditioning regimens. PBSCT was then performed and maintenance IFNa (3 x 10^6 U subcutaneously, 3 times per week) was given until disease progression, severe and persistent side effects, or physician discretion to discontinue IFNa occurred. Three hundred and ninety-nine patients were enrolled in the trial; 101 were excluded during the VAD regimen due to disease progression (39%), severe infectious complications (29%), or multiple other reasons (33%). Two hundred and ninety-eight patients were randomized, 16 of whom were inevaluable for PBSCT because of progression before transplantation (n = 7), patient decision to withdraw (n = 4), death from infection before PBSCT (n = 2), protocol violation (n = 2), or suicide (n = 1). Thus, 282 patients were evaluable for outcomes after PBSCT.

Duration of neutropenia, thrombocytopenia, hospitalization, and use of intravenous antibiotics were all significantly shorter in the MEL group (all comparisons, $P < .001$). Platelet and red blood cell transfusion requirements also were significantly less in the MEL group (both $P < .001$). Grade 3-4 mucositis was less frequent in the MEL group (30% versus 51%; $P < .001$). The CR rate was not different between the two arms (35% MEL versus 29% MEL plus TBI; $P = .41$); the CR plus very good PR rate was slightly higher in the MEL group (55% versus 43%: $P = .06$). At a median follow-up of 20.5 months in the MEL group and 20 months in MEL plus TBI group, the 45-month OS rate was 65.8% in the MEL group versus 45.5% in the MEL plus TBI group ($P = .05$), the median OS was not yet reached in the MEL group and was 43 months in the MEL plus TBI group (Figure 6). Median EFS was not significantly different: 20.5 months in the MEL group versus 21 months in the MEL plus TBI group, $P = .6$ (Figure 7).

Seven studies have described the feasibility and efficacy of novel conditioning regimens [74-83]. Five studies have ret-

Table 10. *Comparison of Patient Characteristics and Outcomes from Articles Included in Autologous SCT Conditioning Regimen Section*

Reference	Quality of Evidence*	Conditioning Regimen (number of patients; dose)	Upper Age Limit (Median; number in category)	DS Stage III	TRM	Median F/U (mos)	Strength of Evidence—OS*	Median OS (mos)	Strength of Evidence—EFS*	Median EFS (mos)
Moreau et al. [73]	I	Mel 200 (142) vs.	65 (61)	75%	0%	20.5	I†	NYR	3	20.5
		Mel 140 TBI 800 (140)	65 (60)	79%	4%	20		43		21
Tribalto et al. [74]	2-I	Bu 16 Mel 60 (39)	60 (49)	48%	3%	55	NC	57	NC	21
Meloni et al. [76]	2-I	Ida Bu Mel 60 (28)	69 (55)	57%	0%	20	NC	NS	NC	NS
Mansi et al. [77]	2-I	Bu 8 or 16 (15)	64 (52)	NS	20%	7	NC	8	NC	NS
Long et al. [78]	2-I	VCTBI (12) or CBV (22)	65 (49)	47%	6%	38	NC	NS	NC	NS
Shimoni et al. [80]	2-I	TtBuC (120)	67 (48)	57%	13%	29	NC	NS	NC	NS
Alegre et al. [82]	2-I	Bu 12Mel 140 (24)	60 (48)	79%	4%	20	NC	NS	NC	NS
Ventura et al. [83]	2-I	CBV (11)	NS	NS	9%	NS	NC	12+	NC	NS
Barlogie et al. [84]	2-2	Mel 100 (46) vs.	NS	NS	28%	108	I‡	4.8	I§	2.4
		Mel 100+GM (24) vs.			17%			21.6		6
		Mel 140ABMT (8) vs.			13%			8.4		4.8
		Mel 140TBIABMT (37) vs.			11%			33.6		15.6
		TtTBIABMT (18)			0%			22.8		7.2
Bensinger et al. [85]	2-I	Bu 14-16 C 120-174 (18) vs.	66 (51)	43%	28%	31.2	NC	NS	NC	NS
		Bu 14 C 120 TBI 600-1050 (36) vs.			14%					
		Bu 12 Mel 100 Tt500 (9)			11%					
Goldschmidt et al. [86]	2-I	Mel 200 (50) vs.	65 (54)	80%	0%	16	NC	NS	NC	NS
		Mel140TBI (50)	60 (50)	72%	4%					
Chen et al. [88]	2-2	VMelTBI (94)	NS	NS	14%	11.8	NC	NYR (58+)	NC	NS
		BuCy (32)			3%					
Lahuerta et al. [89]	2-2	Mel 200 (472)	55‖	68%	4%	NS	3	46	3	22
		Mel 140TBI (135)	49‖	68%	8%			39		20
		BuMel (186)	50‖	66%	6%			57		30
		BuC (28)	53‖	66%	0%			39		23
Desikan et al. [91]	2-2	Second SCT:								
		Mel 200 (43)	NS	NS	0%	NS	I¶	76	I#	61
		Mel 200Cy 120 (19)			0%			39		27
		Mel 140TBI 1125 (24)			8%			25		15

Bu indicates Busulfan; Mel, melphalan; Ida, Idarubicin; V, Etoposide; C, Cyclophosphamide; TBI, total body irradiation; B, carmustine; Tt, thiotepa; GM, GM-CSF; ABMT, autologous bone marrow transplantation; Second SCT, conditioning regimen for first transplantation was Mel 200 whereas the second transplantation regimen varied as indicated; DS, Durie-Salmon; F/U, follow-up; OS, overall survival; EFS, event-free survival; NC, no comparison given in article; NS, not stated in original article; NYR, not yet reached.

*Quality of Evidence definitions are listed in Table 1; Strength of Evidence definitions are listed in Table 2; †$P = .05$ comparing the rate of 45-month OS: 65.8% (MEL) vs. 45.5% (MEL plus TBI); ‡$P = .0004$; §$P = .0001$; ‖means not medians, upper limit not stated; ¶$P = .003$ comparing Mel200 vs. other; #$P < .0001$ comparing Mel200 vs. other.

rospectively compared SCT conditioning regimens for single transplantations [84-90], one study for tandem transplantation [91]. Bensinger et al. reported busulfan plus MEL plus thiotepa had significantly lower TRM than busulfan plus Cy or busulfan plus Cy plus TBI [85] and Chen et al. reported a significantly higher TRM with etoposide plus MEL plus TBI compared with busulfan plus Cy [88]. Three studies found no significant differences between conditioning regimens [84,86,87,89,90], in which one performed 1-, 2-, 4-, and 6-month landmark multivariate analyses [84] and one found no significant independent prognosis for OS or EFS by conditioning regimen in a multivariate analysis of registry data [89,90]. Desikan et al. retrospectively compared conditioning regimens for the second SCT of a planned tandem transplantation and determined EFS ($P < .0001$) and OS ($P = .003$) rates were significantly better in patients who received MEL (200 mg/m^2) versus MEL (200 mg/m^2) plus Cy or MEL (140 mg/m^2) plus TBI [91].

Autologous High-Dose Sequential Therapy

Palumbo et al. investigated an intensified regimen in 68 patients newly diagnosed with MM treated with dexamethasone, Adriamycin, and vincristine (DAV) x 3 cycles for induction therapy [92,93]. Their median age was 65 years (upper limit, 73 years); 64% had stage III disease. Cy (3 g/m^2) was administered on day 0 plus G-CSF on days 3 to 9, followed by PBSC collection on day 10, MEL (60 mg/m^2) on day 11, and PBSC re-infusion on day 12 (CM regimen). The CM regimen was given a total of 3 times at 6-month intervals. By intent-to-treat, 50% (34/68) of patients completed the program. Reasons for failure to complete 3 CM regimens were as follows: relapse (n = 14), low CD34+ cell yield (n = 8), toxicity during CM regimen (n = 7), toxicity after DAV (n = 4), and secondary neoplasm (n = 1). By intent-to-treat, CR was induced in 27% of patients; CR plus PR was induced in 85%. TRM was 3%; median EFS was 35.6 months.

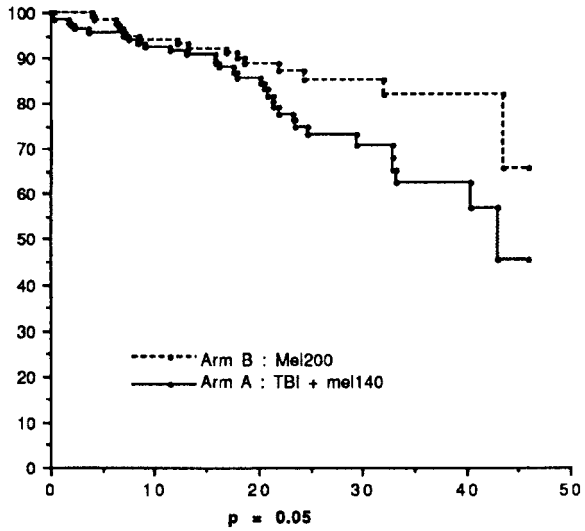

Figure 6. Survival according to treatment arm. Reprinted with permission [73].

Prognostic Factors for OS, EFS, CR Rate, and Favorable Engraftment in Patients Treated with Autologous SCT

Table 11 summarizes the prognostic factors described in this section. The following independent risk factors for longer OS after SCT for MM have been described: non–plasmablastic morphology [94], attainment of CR posttransplantation [95], low B2M [96,97], IgG isotype of MM [96,98], high glomerular filtration rate [99], disease status at time of SCT (in CR or having chemotherapy-responsive disease) [96,97,100-103], MEL-containing conditioning regimen [101], male gender [101], stage I disease at diagnosis [101], C-reactive protein [103], early absolute lymphocyte count recovery [104], plasma cell labeling index [104], circulating plasma cells [104], no deletion of chromosome 13q14 [105], and normal cytogenetics [106].

The following factors have been investigated for correlation with OS or EFS and found not to be significantly associated: number of re-infused plasma cells (EFS) [107]; light chain associated amyloidosis (OS/EFS) [108]; and magnetic resonance imaging 1 month before and after SCT (OS) [109].

In multivariate analyses of tandem PBSCT, a higher rate of continuous CR was associated with low B2M, low C-reactive protein (CRP), no chromosome 13 abnormalities, and less than 1 year of prior chemotherapy [110]. Longer EFS and OS was associated with the absence of any chromosomal abnormalities [111,112], absence of chromosome 11 and 13 abnormalities [113], low B2M [111-113], low CRP [112], attainment of CR [112], 2 PBSCTs given within a 6-month period [112], and shorter duration of chemotherapy before first SCT [111,113].

The following independent risk factors for rapid/favorable engraftment after SCT for MM have been described: Cy plus G-CSF (versus G-CSF alone) as the PBSC mobilization regimen and no prior oral MEL exposure predicted rapid platelet engraftment [114]; no prior high-dose MEL exposure and >2 x 10^6 CD34+ cells/kg infused predicted favorable neutrophil and

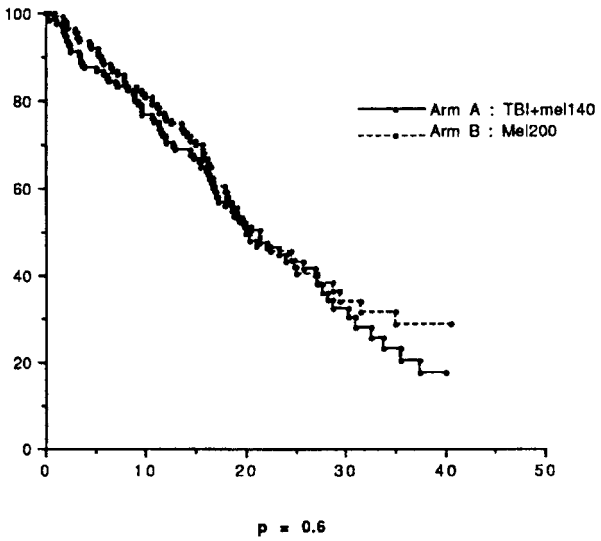

Figure 7. Event-free survival according to treatment arm. Reprinted with permission [73].

Table 11. *Summary of Prognostic Factors for OS, EFS, CR Rate, and Favorable Engraftment in Patients Treated with Autologous SCT*

Reference No.	Factors
Independent laboratory indicators of prolonged OS	
94	Non-plasmablastic morphology
3,70,96,97	Low B2M
103	Low C-reactive protein
96,98	IgG isotype
99	High glomerular filtration rate
104	Early absolute lymphocyte count recovery
105	No deletion of chromosome 13q14
106	Normal cytogenetics
Independent clinical indicators of prolonged OS	
16,96,97,100-103	Disease status at time of SCT (in CR or with chemotherapy-responsive disease)
14,15,16	SCT as de novo therapy (vs. salvage)
7,95	Achievement of CR post-SCT
21,24	Autologous SCT (vs. allogeneic)
101	Melphalan-containing conditioning regimen
101	Male gender
101	Stage I disease at diagnosis
11	Younger age
Clinical and laboratory indicators that are not significant predictors of OS or EFS	
107	Number of reinfused plasma cells (EFS)
108	Light chain associated amyloidosis (OS/EFS)
109	Magnetic resonance imaging pattern 1 mo before and after SCT (OS)
Clinical and laboratory indicators in tandem PBSCT	
	Higher CR rate
110	Low B2M
110	Low C-reactive protein
110	No chromosome 13 abnormalities
110	Less than 1 y of prior chemotherapy
	Prolonged OS and EFS
69,71,111-113	Absence of chromosomal abnormalities
69-71,111-113	Low B2M
112	Low C-reactive protein
112	Attainment of CR
112	Two PBSCTs given within a 6-month period
111,113	Shorter duration of chemotherapy before first PBSCT
Clinical and laboratory indicators for favorable/rapid engraftment after SCT	
	Platelet engraftment
114	Cy+G-CSF (vs. G-CSF alone) as SC mobilization regimen
114	No prior oral MEL exposure
	Neutrophil and platelet engraftment
115	No prior MEL exposure
115	$>2 \times 10^6$ CD34+ cells/kg infused
116	Duration of prior chemotherapy
116	Number of CD34+ cells infused
116	$\leq$24 months of prior chemotherapy needs $\geq 2.0 \times 10^6$ CD34+ cells/kg
116	>24 months of prior chemotherapy needs $\geq 5.0 \times 10^6$ CD34+ cells/kg

platelet recovery [115]; and the number of CD34+ cells/kg infused and duration of exposure to chemotherapy significantly correlated with neutrophil and platelet engraftment [116]. Patients with $\leq$24 months of chemotherapy required $\geq 2.0 \times 10^6$ CD34+ cells/kg; however, patients with >24 months of prior chemotherapy required $\geq 5.0 \times 10^6$ CD34+ cells/kg to achieve rapid neutrophil and platelet engraftment [116].

Other observations include the following: plasma cell labeling index was significantly higher in patients with abnormal cytogenetics [107,117]; prolonged prior therapy with alkylating agents (more than 1 prior cycle of chemotherapy before SC mobilization) was associated with developing myelodysplastic syndrome (MDS) posttransplantation [118]; elevated plasma cell light chain ratio (LCR) in the first 60 days post-SCT most likely indicated residual tumor and not early relapse, however, an elevated LCR >90 days post-SCT significantly correlated with disease progression [119]; failure to achieve CR (as measured by electrophoresis and immunofixation) after SCT was independently predicted by prior therapy with 2 or more chemotherapy regimens, non-responsive disease at time of SCT, and TBI-containing conditioning regimen [120].

Table 12. *Comparison of Patient Characteristics and Outcomes from Articles Included in the Allogeneic SCT Section*

Reference No.	Quality of Evidence*	Number of Patients in Study	Upper Age Limit (Median)	DS Stage III	TRM	Median F/U (mos)	Strength of Evidence—OS*	Median OS (mos)	Strength of Evidence—EFS*	Median EFS (mos)
Gahrton et al. [123]	2-2	90	55 (42)	68%	NS	79 (mean)	NC	26	NC	NS
LeBlanc et al. [127]	2-1	37	53 (47)	68%	16%†	40	NC	NS	NC	NS
Reece et al. [128]	2-1	26	54 (43)	81%	19%‡	14	NC	NS	NC	NS
Majolino et al. [129]	2-1	10	53 (45)	80%	20%†	16.5	NC	NYR (14+)	NC	NS

DS indicates Durie-Salmon; TRM, treatment-related mortality; F/U, follow-up; OS, overall survival; EFS, event-free survival; NC, no comparison given in article; NYR, not yet reached.

*Quality of Evidence definitions are listed in Table 1; Strength of Evidence definitions are listed in Table 2; †TRM by day 120 post-SCT; ‡TRM by day 100 post-SCT.

SYNGENEIC SCT

Gahrton et al. performed a retrospective case-matched analysis of 25 patients with MM treated with BMT (n = 24) or PBSCT (n = 1) from syngeneic donors to 125 autologous SCT patients and 125 allogeneic SCT patients reported to the EBMT Registry [121]. Matching criteria was based on previously identified prognostic factors. For autologous SCT, factors used for matching were number of prior therapies (0-1 versus ≥2), disease status at time of SCT (CR versus PR versus no response/progressive disease), and the nearest possible date of SCT. For allogeneic SCT, factors used for matching were number of prior therapies (0-1 versus ≥2), gender of the recipient, and nearest possible date of SCT. Five autologous SCT and five allogeneic SCT patients were matched to each syngeneic SCT. Compared with autologous SCT patients, syngeneic SCT patients had an improved median OS (73 versus 44 months; $P = .10$), significantly better median PFS (72 versus 25 months; $P = .0088$), and significantly lower risk of relapse (36% versus 78% at 48 months; $P = .0094$). Compared with allogeneic SCT patients, syngeneic SCT patients had a significantly better median OS (73 versus 16 months; $P = .0083$), significantly better median PFS (72 versus 9 months; *P* value was "significantly different" but was not stated quantitatively), but had no difference in the relapse rate (36% versus 40% at 48 months; $P = .99$). The overall TRM rate was >40% in the allogeneic SCT group and 8% in the syngeneic SCT group, but was not stated in the autologous SCT group.

Bensinger et al. described 11 patients with MM given salvage therapy with a BMT (n = 10) or PBSCT (n = 1) from syngeneic donors [122]. Median age was 48 years (range, 36 to 61 years), 10 patients had stage III disease and 2 patients had chemotherapy-sensitive disease at the time of SCT. Median time from diagnosis to SCT was 353 days (range, 176 to 6118 days). Conditioning regimens included Cy plus TBI (1200 cGy in 6 fractions; n = 8), busulfan plus Cy (n = 1), busulfan plus Cy plus TBI (750 cGy in 5 fractions; n = 1), or busulfan plus MEL (100 mg/m^2) plus thiotepa (n = 1). Two patients (18%) died within 100 days post-SCT of transplant-related causes. Five patients (45.5%) achieved a CR post-SCT; however, 3 of these patients relapsed on days +539, +737, and +1706, respectively, and subsequently died. One patient died of secondary MDS; 2 patients are long-term survivors (9+ and 15+ years).

ALLOGENEIC SCT

Table 12 summarizes the evaluation of the quality and strength of the evidence, patient characteristics, and outcomes of the articles reviewed in this section.

Gahrton et al. retrospectively reviewed 90 patients who received allogeneic BMTs from HLA-identical sibling donors and were reported to the EBMT Registry between 1983 and 1989 [123-126]. Median time from diagnosis to BMT was 19 months (range, 3 to 85 months). For induction therapy, 32 patients received intermittent MP and 58 patients received 1 of 32 different drug combinations, most containing either MEL or Cy plus other drugs. At the time of allogeneic BMT, 7 (8%) patients were in CR, 34 (38%) in PR, and 49 (54%) were non-responders or had progressive disease. Conditioning regimens were Cy plus TBI (n = 33), Cy plus TBI plus other drug combinations (n = 43), MEL plus TBI (n = 5), Cy plus busulfan (n = 6), MEL plus Cy (n = 2), and Cy plus other drugs (n = 1). GVHD prophylaxis consisted of methotrexate plus cyclosporine (n = 34), cyclosporine alone (n = 10), methotrexate plus cyclosporine plus prednisolone (n = 7), cyclosporine plus prednisolone (n = 3), methotrexate alone (n = 3), or methotrexate plus prednisolone (n = 2). Thirty-one patients received T-cell depleted BM grafts with or without additional GVHD prophylaxis regimens.

Eighteen patients (20%) died before engraftment. By intent-to-treat, 39 (43%) achieved a CR post-BMT and 8 (9%) developed grade III or IV acute GVHD. Median OS was 26 months. No pretreatment factors significantly predicted OS, although there were trends toward improved OS in patients who had stage I disease, were in CR at time of BMT, had received only 1 prior chemotherapy regimen, and underwent BMT within 12 months of diagnosis. Remission status post-BMT (ie, patients who achieved CR) significantly predicted longer OS ($P = .0001$) as did grade I acute GVHD ($P = .004$). At an average of 79 months after the start of the study, 43 patients have died of various causes including interstitial pneumonia (n = 9), MM (n = 8), acute GVHD (n = 6), bacterial or fungal infections (n = 6), hemorrhage (n = 5), organ failure (n = 4), graft failure (n = 2), adult respiratory distress syndrome (n = 2), or secondary leukemia (n = 1).

LeBlanc et al. reported on 37 patients with MM treated with an allogeneic BMT (n = 18) or PBSCT (n = 19) from HLA-

identical (6/6 match) (n = 37) or single antigen mismatched (5/6 match) (n = 1) sibling donors between 1990 and 2000 [127]. The median number of prior chemotherapy regimens was 1 (range, 1 to 4) including 6 patients who had undergone a prior autologous SCT. Median time from diagnosis to SCT was 9.3 months (range, 4 to 41 months), with 17 (46%) patients in CR and 9 (24%) in PR at the time of SCT, whereas 6 (16%) had stable disease and 5 (14%) were unevaluable. Conditioning regimens consisted of Cy plus TBI (n = 25), busulfan plus Cy (n = 7), MEL plus TBI (n = 3), busulfan plus Cy plus MEL (n = 1), or BCNU plus etoposide plus cytosine arabinoside plus CY (n = 1). GVHD prophylaxis comprised cyclosporine and methotrexate. Nine patients (24%) developed grade III or IV acute GVHD; 14 (38%) developed extensive chronic GVHD. Twenty-five patients (68%) were evaluable for response, but, by intent-to-treat analysis, 41% (15/37) achieved a CR post-allogeneic SCT, 19% (7/37) achieved a PR, and 8% (3/37) died of progressive disease. The Kaplan-Meier estimate of OS at 40 months was 32%.

Reece et al. studied 26 patients with MM treated with allogeneic BMT from an HLA-matched sibling (n = 19), HLA-mismatched relative (n = 3), or unrelated (n = 4) donor [128]. Median time from diagnosis to BMT was 4 months (range, 2-58 months) with a median 1 prior chemotherapy regimen (range, 1-5). At the time of allogeneic BMT, 21 patients (81%) had chemotherapy-sensitive disease. Conditioning regimens consisted of busulfan plus Cy plus MEL (n = 14), busulfan plus Cy (n = 8), or Cy plus TBI (n = 4), and GVHD prophylaxis consisted of cyclosporine plus methotrexate with or without XomaZyme (n = 21) or cyclosporine plus methylprednisolone (n = 5). Acute GVHD grade II to IV occurred in 20 patients and was fatal in 3 patients. Of the 26 allogeneic BMT patients, 13 (50%) achieved a CR, 6 (23%) a PR, 2 (8%) had no response, and 5 (19%) were not evaluable for disease response posttransplantation. At a median follow-up of 14 months, the 3-year OS and PFS rates were 46.5% (95% CI, 20%-69%) and 40% (95% CI, 19%-61%), respectively. The PFS rate of the patients with chemotherapy-resistant disease at time of BMT was significantly lower than patients with chemotherapy-sensitive disease at time of BMT (0% versus 52%; $P = .0066$).

Majolino et al. studied 10 patients with MM who underwent allogeneic PBSCT from HLA-identical sibling donors [129]. At time of PBSCT, 3 patients were in CR, 3 in PR, 3 had relapsed disease, and 1 had progressive disease. Donor PBSCs were mobilized with G-CSF (n = 6) or GM-CSF followed by G-CSF (n = 4). Conditioning regimens included busulfan plus MEL (n = 9) or busulfan plus Cy (n = 1). All patients received cyclosporine plus methotrexate as GVHD prophylaxis. Acute GVHD grade II developed in 3 patients and grade III developed in 1 patient. Eight patients achieved a CR and 2 achieved a PR post-PBSCT. At a median 18.5 months post-PBSCT, 8 patients were alive, including 6 in CR.

Allogeneic PBSCT versus BMT

Gahrton et al. retrospectively compared 690 patients who underwent allogeneic transplantation reported to the EBMT Registry between 1983 and 1998, including 334 BMTs between 1983 and 1993 (historic BMT group), 223 allogeneic BMTs between 1994 and 1998 (concurrent BMT group), and 133 PBSCTs between 1994 and 1998 (PBSCT group) [130]. Time to neutrophil and platelet engraftment did not differ between the historic and concurrent BMT groups, whereas engraftment times in the PBSCT group were significantly shorter when compared with either the historic or concurrent BMT groups. The incidence of acute and chronic GVHD was not significantly different between the 3 groups: grade III/IV acute GVHD 16% historic BMT versus 11% concurrent BMT versus 18% PBSCT groups; chronic GVHD 27% versus 11% versus 17%, respectively. The authors postulate the rate of chronic GVHD was higher in the historic BMT group due to a longer follow-up period, although the specific median follow-up times for the 3 groups were not stated in the report. Median OS was significantly prolonged in the concurrent BMT group compared with the historic BMT group (50 months versus 10 months; $P < .0001$), but there was no significant difference between the PBSCT (median OS not yet reached) and concurrent BMT groups. TRM at 6 months was significantly reduced in the concurrent versus historic BMT groups (6-month TRM rate, 38% versus 21%) but was not significantly different between the PBSCT and concurrent BMT groups (the TRM rate for the PBSCT group was not stated in the original article). Median PFS was significantly longer in the concurrent BMT group compared with the historic BMT group (19 months versus 7 months; $P < .0001$) but did not significantly differ between the concurrent BMT and PBSCT (15 months) groups.

Allogeneic SCT Conditioning Regimens

Cavo et al. investigated the feasibility and efficacy of busulfan (16 mg/kg) plus Cy (200 mg/m^2) as an alternative conditioning regimen for allogeneic BMT with HLA-compatible sibling donors in 19 patients with MM [131]. Twelve (63%) patients failed to respond to prior chemotherapy, whereas 7 (37%) had chemotherapy-sensitive disease. GVHD prophylaxis was cyclosporine plus methotrexate (n = 16) or T-cell depletion plus Campath with or without cyclosporine (n = 3). Neutrophil recovery was achieved by 18 (95%) patients at a median of 18 days (range, 12 to 22 days) post-allogeneic BMT; graft failure occurred in 1 T-cell depleted allogeneic BMT patient who died of cerebral hemorrhage on day +36. Six patients (33%) developed grade II to IV acute GVHD; 1 patient each had limited or extensive chronic GVHD. Six patients died of treatment-related complications before day 100. At a median follow-up of 66 months, 14 patients have died of progressive MM (n = 7) or treatment-related causes (n = 7). Median OS was 21 months and median EFS was 12 months. Chemotherapy sensitivity was a significant predictor of prolonged OS (4-year OS rate, 71% versus 0%; $P = .0004$) and EFS (4-year EFS rate, 57% versus 0%; $P = .01$).

Badros et al. reported on 31 patients with MM given allogeneic PBSCT with a non-myeloablative conditioning regimen and an HLA-compatible sibling (n = 25) or unrelated (n = 6) donor [132]. All but 1 patient had received 1 (n = 13) or ≥2 (n = 17) prior autologous transplantation. The non-myeloablative conditioning regimen was MEL (100 mg/m^2) for related allografts and MEL (100 mg/m^2) plus TBI (250 cGy) plus fludarabine (30 mg/m^2) for unrelated allografts. Patients with related donors received unmanipulated PBSCs collected after G-CSF mobilization. Among patients with unrelated donors, 3 received PBSCs collected after G-CSF mobilization (2 of whom were CD34+ selected/T-cell depleted) and 3 received unmanipulated, unmobilized BM. GVHD prophylaxis consisted of cy-

Table 13. *Summary of Prognostic Factors for PFS, OS, and EFS in Patients Treated with Allogeneic SCT*

Reference No.	Factors
Statistically significant independent indicators of prolonged PFS	
126	Chemotherapy-sensitive disease at time of SCT
134	<Stage III disease
Statistically significant independent indicators of prolonged OS	
123,133	Achievement of CR post-SCT
123	Grade I acute GVHD
133	<Grade III acute GVHD
134	Chemotherapy-sensitive disease at time of SCT
134	Low B2M (<2.5 g/L)
134	Less than 1 y between diagnosis and SCT
127	Fewer cycles of chemotherapy prior to allogeneic SCT
Statistically significant independent indicators of prolonged EFS	
131	Chemotherapy-sensitive disease at time of SCT
135	No prior autologous SCT
135	Creatinine clearance > 100 mL/min

closporine for related allografts and cyclosporine plus methylprednisolone for unrelated allografts. Patients with no evidence of GVHD were initially scheduled to receive donor lymphocyte infusions (DLIs) on days +21, 42, and 112 to achieve full chimeric engraftment. The duration of cyclosporine was doubled, however, due to a high incidence of GVHD, after which 18 patients were given DLIs based on disease and chimerism status.

One patient with a related donor and 2 patients with unrelated donors died of TRM before day +100 post-allogeneic SCT. Two patients failed to demonstrate myeloid engraftment even after a second allogeneic PBSC infusion; both received an autologous PBSC rescue with 1 alive in near CR and 1 dead of progressive disease. The remaining patients achieved neutrophil recovery at a median of 14 days (range, 10 to 46 days) and platelet recovery at a median of 15 days (range, 0 to 50+ days) post-allogeneic PBSCT. Eighteen patients developed grade II to IV acute GVHD, 12 of whom developed acute GVHD after DLI. Ten patients developed chronic GVHD, 6 with extensive involvement. Twenty-two patients (71%) had at least a PR to the allograft. At a median follow-up of 6 months (range, 1.5 to 24 months), 19 patients are alive in CR or near CR. The median OS was 15 months.

Patients given nonmyeloablative conditioning (n = 31) were compared with historical controls treated with myeloablative regimens (n = 93, mostly TBI-based regimens). TRM in the first 100 days post-allogeneic SCT was significantly lower in the nonmyeloablative regimen group (10% versus 29%; $P = .03$). A multivariate analysis determined nonmyeloablative conditioning regimen to be the only clinical risk factor predictive of prolonged OS ($P = .007$).

Prognostic Factors for PFS, OS, and EFS in Patients Treated with Allogeneic SCT

Table 13 summarizes the prognostic factors described in this section. Gahrton et al. analyzed the prognostic factors for allogeneic BMT using matched sibling donors in 162 patients with MM reported to the EBMT Registry between 1983 and 1993 [133]. Patients were heterogeneous with respect to pretransplantation disease characteristics, duration and regimens of prior chemotherapy, conditioning regimens, GVHD prophylaxis, and supportive care. By univariate analysis, favorable predictors of OS were female gender ($P = .04$), stage I disease at diagnosis ($P = .05$), 1 prior chemotherapy regimen ($P = .02$), in CR at time of BMT ($P = .05$), achievement of CR post-BMT ($P = .001$), and no grade III or IV acute GVHD ($P = .02$). Trends toward significance were found for IgA subtype MM ($P = .08$) and low B2M (<4 g/L; P value not stated). Multivariate analysis failed to identify any statistically significant independent pre-BMT predictors of OS (the strongest tendency was for female gender; $P = .07$). Multivariate analysis identified acute GVHD grade III or IV ($P = .0006$) as the most significant post-BMT factor with an adverse effect on OS, whereas a significant positive effect on OS was identified in patients who achieved a CR post-BMT ($P = .01$).

Bensinger et al. determined the prognostic factors for 80 patients with MM treated with allogeneic BMT from related (n = 71) or unrelated (n = 9) donors between 1987 and 1994 [134]. Conditioning regimens were busulfan plus Cy (n = 57) or busulfan plus Cy plus TBI (n = 23). GVHD prophylaxis consisted of cyclosporine plus methotrexate (n = 46), cyclosporine plus methylprednisolone (n = 22), FK506 (Tacrolimus) (n = 8), cyclosporine alone (n = 3), or T-cell depletion (n = 1). TRM within 100 days post-BMT was 44% (35/80). Statistically significant risk factors for adverse outcome by multivariate analysis were elevated B2M (>2.5 g/L: $P = .009$) and time from diagnosis to transplantation greater than 1 year ($P = .033$). Factors that were considered in the multivariate model but that were not significant independent predictors were age, sex, number of chemotherapy cycles and regimens, plasma cells >10%, prior radiation therapy, stage III disease, chemotherapy sensitivity, TBI-containing conditioning regimen, and donor type.

Kulkarni et al. identified significant prognostic factors in a study of 33 patients with MM treated with allogeneic BMT (n = 29) or PBSCT (n = 4) from related (n = 29) or unrelated (n = 4) donors between 1981 and 1998 [135]. Conditioning regimens included the following: MEL (110 mg/m^2) plus TBI (single fraction 950-1050 cGy) (n = 22), busulfan plus Cy (n = 3), Cy plus TBI (single fraction 950-1050 cGy) (n = 3), Cy plus MEL plus Campath plus TBI (1200 cGy in 6 fractions) (n = 3), busulfan plus MEL (n = 2), or MEL plus TBI (1200 cGy in 6 fractions) (n = 1). GVHD prophylaxis consisted of cyclosporine plus methotrexate (n = 29) or cyclosporine alone (n = 4). TRM within 150 days post-SCT was 51.5%. Grade III or IV acute GVHD developed in 30% of patients. At a median follow-up of 27 months, the 2-year EFS rate was significantly less in patients who had a prior autologous SCT compared with those who did not (16.7% versus 47.9%; $P = .019$). Patients with a creatinine clearance of >100 mL/min at time of SCT had a significantly improved EFS rate compared with those with ≤100 mL/min (72.7% versus 21.8%; $P = .013$).

Badros et al. retrospectively analyzed the effect of ABO mismatches in 27 patients with MM who received nonmyeloablative conditioning regimens [136]. Three patients had minor and 6 had major ABO mismatched allogeneic grafts. The 3 patients with minor ABO mismatches showed evidence of hemolysis, but all 3 converted to the donor ABO group. Three of the major ABO mismatched patients developed grade II to III

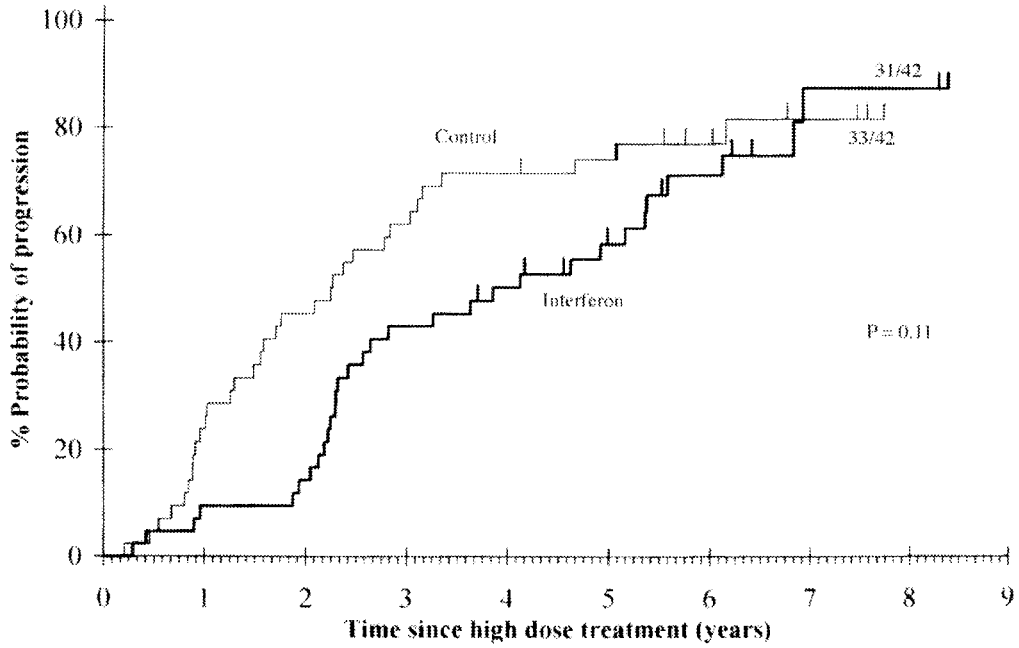

Figure 8. Probability of progression-free survival of all patients by the Kaplan-Meier method. Reprinted with permission [138].

acute GVHD before converting to the donor ABO group, 1 failed to engraft and had autologous reconstitution, 1 developed red blood cell aplasia, and 1 remained a mixed chimera even after 3 DLIs. No ABO-matched patients had graft failure. ABO mismatch did not correlate with OS or incidence of acute GVHD.

THERAPY POST-SCT

IFNa Maintenance Therapy Post-SCT

Attal et al. demonstrated the feasibility and safety of using maintenance IFNa therapy after autologous BMT in a study of 20 patients with MM in first PR [137]. Conditioning regimen was MEL (140 mg/m^2) plus TBI (800 cGy in 4 fractions with no lung shielding). IFNa (3 x 10^6/m^2 subcutaneously 3 times per week) was started when good performance status (World Health Organization <2), granulocytes ≥500 x 10^6/L, and platelet count ≥75 x 10^9/L were achieved (median, 2.7 months post-BMT) and was continued until relapse. No patients died of toxicity from the transplant or IFNa. At a median follow-up post-BMT of 13 months, 18 patients remained progression-free and 2 have relapsed resulting in a 2-year PFS rate of 85%. At last follow-up, all progression-free patients were still receiving IFNa without dose reduction. One patient required a transient interruption in IFNa therapy due to thrombocytopenia.

Cunningham et al. performed a randomized trial to evaluate the role of IFNa maintenance therapy post-BMT [138]. At the time of hematologic recovery (white blood cell (WBC) count >2 x 10^9/L and platelets >100 x 10^9/L, median 62 days post-BMT), 84 patients were randomly assigned to maintenance IFNa administered subcutaneously 3 times per week at a dose of 3 x 10^6 units/m^2 until relapse (n = 42, IFNa arm) or to no further therapy post-BMT (n = 42, control arm). Patients received MEL (100-200 mg/m^2) plus BMT (n = 35 IFNa, 34 control arm), MEL (140 mg/m^2) without stem cell rescue (n = 5 IFNa, 7 control arm), or busulfan (16 mg/kg) plus BMT (n = 2 IFNa, 1 control arm) as conditioning regimen.

At a median follow-up of 52 months, the median PFS after BMT was 46 months in the IFNa arm versus 27 months in the control arm ($P < .025$) and OS after BMT was 88% versus 67%, respectively ($P = .006$). At a median follow-up of 77 months, however, the PFS and OS were not significantly different: 31 patients in the IFNa arm and 33 patients in the control arm relapsed ($P = .11$) (Figure 8) and 17 patients in the IFNa arm and 21 patients in the control arm died ($P = .106$).

Powles et al. studied a consecutive series of 195 patients with newly diagnosed untreated MM aged younger than 70 years from September 1986 to March 1994 [139]. All patients were intended to complete a sequential therapy regimen consisting of induction, high-dose therapy with stem cell support, and maintenance IFNa. A total of 57 patients received IFNa as maintenance, 46 of whom also were enrolled in the randomized trial by Cunningham et al. Median OS and PFS were longer for patients who underwent transplantation who received maintenance IFNa (n = 57) than those who did not (OS: not yet reached at 8 years versus not stated in article; PFS: 44 versus 21 months; $P = .0036$).

Powles et al. also compared the IFNa tolerance of patients who had received autologous BMT (n = 37) with those who received PBSCT (n = 39), and also compared engraftment, response, and survival in autologous BMT (n = 21) with PBSCT (n = 15) patients [140]. Again, these patients overlapped with those in the Cunningham et al. randomized trial and the Powles et al. study discussed above. INFa was initiated at a median of 58 days post-BMT and 61 days post-PBSCT and given 3 times per week at a dosage of 3 x 10^6/m^2 after hematopoietic recovery (WBC count >2 x 10^9/L and platelets >50 x

10^9/L). There was no significant difference between the 2 groups with regard to toxicity. BMT and PBSCT patients had comparable IFNa dose modification, discontinuation of treatment, and break in treatment. PBSCT patients had faster neutrophil engraftment (17 versus 22 days; *P* value not significant) and significantly faster platelet engraftment (15 versus 26 days; $P < .005$) than BMT patients. There was no significant difference between the PBSCT and BMT groups with respect to CR rate (60% versus 80%), 2-year OS rate (79% versus 95%), or 2-year PFS rate (79% versus 81%).

Björkstrand et al. performed a retrospective study of IFNa maintenance therapy after SCT in patients reported to the EBMT Registry between 1988 and 1998 [141]. Patients who received IFNa maintenance, engrafted after a single transplantation, and were in CR or PR 6 months after transplantation (n = 473) were case matched to patients who met the same criteria but who did not receive IFNa maintenance therapy (n = 419). Several prognostic factors were significantly different between the IFNa and no IFNa groups; however, they were statistically corrected for in the multivariate analysis of survival.

Median OS was significantly longer in the IFNa group compared with the no IFNa group (78 versus 47 months; $P = .007$). Patients who were in PR at 6 months posttransplantation retained a significantly longer median OS (97 versus 46 months; $P = .03$), but no difference in median OS was demonstrated for patients in CR at 6 months posttransplantation (64 versus 51 months; $P = .1$). Median PFS also was significantly longer in the IFNa group compared with the no IFNa group (29 versus 20 months; $P = .006$). Patients in PR at 6 months posttransplantation also retained a significantly longer median PFS (31 versus 18 months; $P = .003$), however, patients in CR at 6 months posttransplantation had no difference in median PFS (29 versus 22 months; $P = .6$).

DLI after SCT

Lokhorst et al. studied 27 patients with MM who received 52 DLI infusions at a median of 30 months post-allogeneic SCT from a sibling donor [142,143]. Disease status at time of allogeneic SCT was refractory (n = 11) or PR (n = 16); no patients were in CR at time of allogeneic SCT. In addition, all patients who received DLI were refractory to or relapsed after their allogeneic SCT. GVHD prophylaxis post-SCT consisted of a partially T-cell depleted graft plus cyclosporine (n = 25) or cyclosporine plus methotrexate (n = 2). Patients with active GVHD were ineligible for DLI. DLI T-cell doses ranged from 1 x 10^6 to 5 x 10^8 cells/kg. Patients who had no response by 12 weeks post-DLI were eligible to receive additional DLI courses with escalated T-cell doses.

Eight patients (30%) achieved PR, and 6 (22%) achieved CR after 1 (n = 8), 2 (n = 1), 3 (n = 2), or 4 (n = 3) DLIs. Five patients were still in remission 30+ months post-DLI. Fifteen patients (56%) developed acute GVHD post-DLI, including 4 with grade III GVHD. Seven patients (26%) developed chronic GVHD post-DLI, including 3 patients with extensive chronic GVHD. Median OS of the 27 patients was 18 months with 13 survivors. By multivariate analysis, the only factors predictive of response to DLI were T-cell dose >1.0 x 10^8 cells/kg and PR before allogeneic SCT.

Salama et al. evaluated 25 patients with MM from 15 BMT centers who were treated with 1 to 4 DLIs after allogeneic BMT from matched related (n = 23), mismatched related (n = 1), or matched unrelated (n = 1) donors [144]. Disease status at time of allogeneic BMT was refractory (n = 10), PR (n = 13), relapse (n = 1), or CR (n = 1). Nine patients achieved CR, 10 achieved PR, 5 had no response, and 1 was not evaluable after transplantation. Median T-cell dose for the first DLI was 1.0 x 10^8 cells/kg in 18 patients with available data (range, 0.02-2.24 x 10^8 cells/kg). Nine patients received a second DLI at a median of 16 weeks after the first. Median T-cell dose was 3.3 x 10^8 cells/kg (n = 7 with available data; range, 0.15-5.16 x 10^8 cells/kg). One patient received a third and fourth DLI.

Thirteen of 25 patients (52%) developed acute GVHD including 5 with grade III and 1 with grade IV. Eleven patients developed chronic GVHD, including 5 with extensive involvement. At a median follow-up of 19.5 months, 12 of 25 patients were alive, 2 in CR, and 10 with disease. Thirteen patients died of progressive disease (n = 10), infection (n = 2), or GVHD (n = 1). By univariate analysis, patients given T-cell doses ≥1 x 10^8 cells/kg were more likely to have both GVHD and disease response. Overall, 4 of 25 patients benefited from DLI (disease response lasting at least 12 months), however, 3 had severe acute or extensive chronic GVHD. Three additional patients possibly benefited from DLI (this is the ongoing disease response, but follow-up is <12 months), but 2 of them had significant GVHD. Three patients had a minimal benefit from DLI (disease response <12 months) and 15 patients had no disease response to DLI including 3 with significant GVHD.

Alyea et al. examined 24 patients with MM treated with CD6+ T-cell depleted allogeneic BMT from matched sibling donors followed by prophylactic CD4+ DLI as a single infusion given 6 to 9 months post-BMT in the absence of GVHD and immunosuppressive therapy [145]. Patients received a median of 3 prior chemotherapy regimens (range, 1-7); median time from diagnosis to BMT was 10 months. Conditioning regimens were Cy plus TBI (1400 cGy; n = 21) or busulfan plus Cy (n = 3). T-cell depletion was the only method of GVHD prophylaxis.

All patients achieved neutrophil recovery at a median of 12 days (range, 10 to 17 days) and platelet recovery at a median of 19 days (range, 16 to 28 days) after allogeneic BMT. Day +100 TRM rate was 4%. Five patients (21%) developed grade II to III acute GVHD after BMT. Seven of 14 patients who received DLI developed grade II to IV acute GVHD or extensive chronic GVHD after DLI. At a median follow-up of 2.3 years, the 2-year OS and PFS rates were 55% (95% CI, 34%-76%) and 30% (95% CI, 10%-50%). Patients in the T-cell depleted BMT plus DLI group were compared with a cohort of 38 patients treated with T-cell depleted allogeneic BMT without DLI. There was no significant difference in 1- or 2-year OS or PFS between the 2 groups.

Badros et al. reported 16 patients with MM who received an allogeneic PBSCT from an HLA-matched (n = 14) or mismatched (n = 2) sibling donor using a non-myeloablative conditioning regimen (MEL 100 mg/m^2) followed by 1 (n = 5), 2 (n = 4), or 3 (n = 3) DLIs [146] (update of Badros et al. [132]). Patients had received 1 (n = 9) or 2 (n = 7) prior autologous transplants. At time of allogeneic PBSCT, 10 were in refractory relapse, 4 were in PR, and 2 were in near CR (CR but with positive immunofixation). DLIs were given to 14 patients with

no evidence of GVHD to induce full chimerism (n = 4) or to treat residual disease (n = 10).

One patient who failed to achieve neutrophil engraftment after a second infusion of allogeneic PBSCs was given autologous back-up stem cells that achieved autologous engraftment and a near CR. No patients died of TRM in the first 100 days post-PBSCT. Acute GVHD occurred in 10 patients, including 1 with grade IV; chronic GVHD occurred in 7 patients, including 4 with extensive involvement. At a median follow-up of 12 months, 11 of 16 patients were alive, 5 in CR, 3 in near CR, and 4 in PR. Three patients died of GVHD and 2 of progressive disease.

Second SCT for the Treatment of Relapse after a Prior SCT

Tricot et al. studied 94 patients who relapsed after an autologous transplantation and were treated with either standard-dose salvage therapy (n = 53; VAD, EDAP, high-dose dexamethasone, or other derivatives) or another transplantation (31 autologous and 10 allogeneic) [147]. Seventy-one patients had relapsed after 1 and 23 patients relapsed after 2 prior autologous transplantations. Patients were offered standard salvage chemotherapy if they had no cryopreserved BM or PB or had rapidly progressing disease (plasmablastic transformation, rapid increase in tumor mass, or hypercalcemia). Another transplantation was performed if patients had adequate cryopreserved BM or PB and no rapidly progressing disease. At a median follow-up of 11 months after salvage therapy, patients who received a transplant had a significantly higher CR rate (22% versus 2%; $P = .002$) and OS rate (at 18 months, 78% versus 41%; $P = .009$) than patients who received standard salvage chemotherapy. By multivariate analysis, independent predictors of prolonged OS were pre-salvage B2M $\leq$2.5 mg/L and relapse $>$12 months after the preceding transplantation.

Mehta et al. compared 42 patients treated with an allogeneic SCT after a failed autologous SCT to 42 pair-matched controls who were treated with a second autologous SCT as salvage therapy [148]. Controls were matched for albumin, C-reactive protein, creatinine, disease sensitivity, duration of standard therapy prior to first SCT, Ig isotype, karyotype, LDH, and response to first SCT. Patients given a second autologous SCT were older, had a higher B2M, and a shorter interval between the 2 SCTs than those given a second allogeneic SCT. Approximately half the patients were offered a second transplantation due to failure to achieve at least a PR to the first, and the other half experienced disease progression after their first transplantation.

There was no significant difference between the second allogeneic versus the autologous SCT groups with regard to CR rate (41% versus 33%; *P* not significant) or 3-year EFS rate (20% $\pm$ 8% versus 25% $\pm$ 8%). Second autologous SCT patients had a significantly higher 3-year OS rate (54% versus 29%; $P = .01$) and 3-year probability of disease progression (72% versus 31%: $P = .03$) compared with the allogeneic group. A significantly higher 1-year probability of TRM was demonstrated in patients who received a second allogeneic SCT compared with patients who received a second autologous transplant (43% versus 10%; $P = .0001$).

Garban et al. studied 12 patients with persistent or relapsed MM previously treated with at least VAD plus an autologous SCT who were given a second transplant [149]. The patients, who were not eligible for conventional allogeneic transplantation due to age or poor performance status, received PBSCT (n = 11) or BMT (n = 1) from HLA-matched sibling donors using a nonmyeloablative conditioning regimen consisting of fludarabine, anti-thymocyte globulin, and busulfan. Prior conditioning for the autologous transplantation had been MEL (140 mg/m^2) plus TBI or MEL (200 mg/m^2). Cyclosporine was given for 45 to 90 days after non-myeloablative allogeneic SCT for GVHD prophylaxis.

Four patients achieved CR, 7 achieved PR, and 1 progressed after allogeneic SCT. All patients engrafted, no mucositis occurred, no parenteral feeding was required, and some patients did not require platelet transfusions. Three patients died before day 100, one from progressive disease despite GVHD, one with preexisting cardiopathy died from acute cardiac failure, and one whose cause of death was not given. Six patients developed grade II to IV acute GVHD, and 7 patients developed chronic GVHD (including 2 with extensive involvement). Five patients developed systemic or localized cytomegalovirus (CMV) infection, including one who died 5 months post-SCT from CMV encephalitis.

Singhal et al. reported a study of 88 patients with MM who underwent 1 (n = 10) or 2 (n = 78) prior autologous transplantations and had no available cryopreserved stem cells for additional SCT [150]. Seventy-one patients received IFNa maintenance therapy after the previous transplantation(s), which was discontinued 2 to 3 months prior to subsequent SC collections. Patients were mobilized with G-CSF (median dose 13.4 μg/kg; range, 4.8-24). A median of 3.03 x 10^6 CD34+ cells/kg (range, 0.46-9.16) were collected by apheresis (median number of collections, 5; range, 2-13). The time between preceding transplantation and PBSC collections was a median of 29 months (range, 5-68 months). By multivariate analysis, patients with platelet counts $\geq$200 x 10^9/L ($P < .0001$), no myelosuppressive chemotherapy between last SCT and collections ($P = .02$), and with no (n = 17) or $\leq$6 months (n = 15) of IFNa ($P = .03$) had significantly higher CD34+ cell yields.

Mehta et al. studied 18 patients with MM with relapsed disease after a median of 5 prior regimens (range, 4-10) treated with an autologous PBSCT with cyclophosphamide plus carboplatin plus etoposide (CCV) conditioning regimen [151]. Fifteen patients had received a prior autologous transplant, 2 patients had 2 prior autologous transplants, and 1 patient had received prior autologous and allogeneic transplants. Four patients died from TRM on days –1, 0, 3, and 10 post-PBSCT. Causes of death were acute renal failure with congestive heart failure, cardiac arrest, respiratory failure due to fluid overload, and multi-organ failure, respectively. Of the remaining 14 patients, 1 achieved a CR, 1 a PR, 2 had $>$50% reduction in tumor mass, and the remainder had no response or progressive disease. Nine patients died of relapsed or progressive disease at a median of 7 months post-PBSCT, 5 were alive (1 with stable PR and 4 with progressive disease) at a median of 13 months post-PBSCT.

SCT ECONOMIC/COST-EFFECTIVENESS STUDIES

Lenhoff et al. performed a prospective, non-randomized, population-based, multicenter study of 274 patients with MM comparing autologous PBSCT with MEL conditioning and IFNa maintenance with 274 historical controls pooled from 5

randomized trials of conventional chemotherapy, as previously described [5]. Gulbrandsen et al. reported a companion study that collected data on costs, resource consumption, and health-related quality-of-life (HRQoL) at baseline and during periodic follow-up of the prospective trial; the same method had been used in one of the historical trials including patients treated with MP for induction (n = 70) [152]. In the PBSCT group, 221 patients (78%) participated in the HRQoL study, of whom 201 patients (73%) completed all questionnaires. In the MP group, 66 patients (94%) participated and 61 patients (87%) completed all questionnaires. Quality-adjusted life-years (QALYs) were calculated with the assumption of a mean 1.5-year gain in survival at the cost of a 6-month reduction in the HRQoL.

The PBSCT group had significantly prolonged median OS compared with the MP group (62 versus 44 months). In the PBSCT group, resource consumption included medical costs, hospital stay (including intensive care unit days), personnel costs (physicians and nurses), leukapheresis, and transfusions, and involved a cost of $24,400 (all costs are in year 2000 United States [US] dollars). Indirect costs measuring lost production (estimate of 104 days of lost unpaid employment per person) were estimated at $7,900, for a total societal cost per PBSCT patient of $32,300. The cost-utility ratio for PBSCT over MP was $27,000 per QALY, and by sensitivity analysis ranged from $20,200 to $40,000 per QALY.

Uyl-de Groot et al. retrospectively calculated the treatment costs of 26 patients with MM who received MEL (n = 11) or MEL plus G-CSF (n = 7) compared with autologous transplantation with G-CSF mobilized PBSC re-infused after MEL (n = 8) [153]. Costs included hospital days (personnel, supplies, medical services, and overhead), diagnostics, pharmacy, laboratory, insertion of central venous catheters, and transfusions. The PBSCT group had significantly lower costs for hospital days (US $7,335 versus $16,747; $P < .005$), antibiotics ($2,454 versus $6,476 ; $P < .01$), parenteral nutrition ($229 versus $2,148 ; $P < .001$), transfusions ($1,065 versus $2,762; $P < .05$), and total treatment costs ($17,908 versus $32,223; $P < .005$) compared with the MEL +/- G-CSF group. The PBSCT group had significantly higher costs for G-CSF ($5,293 versus $1,393: $P < .01$) compared with the MEL +/- G-CSF group. The article does not state what calendar year the costs in US dollars represent, although the article was submitted to the journal in 1993.

Henon et al. retrospectively compared the survival, quality of life, and therapy costs of 12 patients with MM stage III treated with MEL as induction and mobilization, PBSC collections, and autologous transplantation (group 1) with 10 patients with similar characteristics but treated with conventional chemotherapy (group 2) with 15 patients with MM stage II treated with conventional chemotherapy (group 3) [154]. The conventional chemotherapy regimen consisted of at least 6 cycles of either VAD or M2 (BCNU, eldisine, Cy, and MEL); the conditioning regimen was MEL (140 mg/m^2) plus TBI. Group 1 patients did not receive any maintenance therapy post-PBSCT; they were treated at time of relapse with one of the conventional chemotherapy regimens listed above or with subcutaneous IFNa plus pulse dexamethasone. Group 2 patients surviving at 6 months post-induction therapy received maintenance therapy with the regimen they did not initially receive (VAD or M2). Group 3 patients were treated with MP as maintenance therapy in case of disease response and conventional chemotherapy in case of disease progression.

The average total costs (all in 1993 US dollars) for each group including all therapy as defined above was significantly higher in group 1 ($56,700) versus group 2 ($46,555; $P < .05$) versus group 3 ($37,430; $P < .02$). The average total costs of therapy based on mean survival duration in group 1 was significantly lower ($350/wk) compared with group 2 ($1,862/wk: $P < .0001$) but significantly higher than group 3 ($225/wk; $P < .05$). When these values were adjusted for quality of life, group 1 cost $74/wk more than group 2 and $966/wk more than group 3.

Duncan et al. performed a cost-minimization analysis of 51 patients with MM comparing autologous BMT (n = 14) versus PBSCT (n = 37) [155]. All patients received induction therapy with VAMP, C-VAMP, or verapamil, Cy, vincristine, adriamycin, and methylprednisolone (VC-VAMP) followed by MEL (200 mg/m^2) and infusion of either BM or PBSC. The PBSCT group had a significantly faster time to neutrophil engraftment (16 versus 22 days; $P = .0019$) and time to platelet recovery (19 versus 27 days; $P = .0019$), which resulted in a shorter duration of intravenous antibiotics (12 versus 19 days; $P < .0001$), reduced number of platelet transfusions (12 versus 31.5 units; $P = .0005$), and shorter hospital length of stay (19 versus 27.5 days; $P < .0001$). The total cost of PBSCT was 27.5% less than autologous BMT (actual costs are stated in British pounds with no conversion to US dollars and no calendar year indicated).

Jagannath et al. compared 91 patients with MM who received a total of 118 transplants as outpatients with 160 patients with MM who received 218 transplants as inpatients [156]. Patients treated as outpatients were younger, had a higher percentage of CD34+ cells in the apheresis product, and were more likely to have a normal serum albumin level, low B2M level, and chemotherapy-sensitive disease than inpatients. There was no significant difference in the hematologic recovery between inpatients and outpatients. Twenty-one percent of patients who underwent outpatient transplantations required admission after transplantation for nauseau, vomiting, diarrhea requiring parenteral alimentation and/or severe mucositis requiring narcotic analgesics (28%), bacteremia or pneumonia (28%), febrile neutropenia and gastrointestinal toxicity (24%), persistent fever for more than 3 days (12%), or were admitted at the discretion of the physician (8%). B2M >2.5 mg/L was the only significant risk factor for hospital admission in the outpatient transplant group (58% versus 24%; $P < .001$). Median hospital length of stay was 9 days for outpatients versus 15 days for inpatients ($P = .0001$).

Total charge for the transplantation procedures included physician, hospital, and clinic charges. A multivariate analysis assessing age, gender, prior response to therapy, time from diagnosis to first transplantation, Ig isotype, disease stage, number of CD34+ cells infused, serum creatinine, albumin, B2M, and LDH was performed to identify factors associated with savings. Outpatient transplantation was the only factor associated with savings. Total average adjusted charges were $13,172 (1994 US dollars) lower for outpatients compared with inpatients. Specifically, outpatients had lower hospital-

ization charges (50% of overall savings), pharmacy charges (42%), and pathology/laboratory charges (37%). Outpatients had higher miscellaneous charges (-30% of overall savings) including housing and caregiver costs.

Bujit et al. calculated the treatment and follow-up costs in a retrospective study of 29 patients with newly diagnosed MM [157]. Costs included those for hospitalization, outpatient visits, laboratory, pharmacy, pathology, imaging (X-rays, computed tomography, etc.), apheresis, transfusions, insertion of central venous catheters, personnel, supplies, medical equipment, and overhead. All prices are stated in 1995 US dollars. Each patient was scheduled to be treated and followed in 8 phases (mean cost for each phase and number of patients completing that phase): VAD or VAMP induction ($8,400; n = 29), follow-up I ($425; n = 29), MEL plus whole blood rescue ($11,000; n = 29), follow-up II ($1,825; n = 26; 3 patients died during this phase), PBSC collections ($9,350; n = 21), follow-up III ($1,250; n = 17; 1 patient died during this phase), autologous PBSCT with busulfan plus Cy conditioning ($15,125; n = 15; 2 patients died during this phase), and follow-up IV until 3 months post-hospital discharge after PBSCT ($2,400; n = 13). The total mean costs of treatment and follow-up for the 13 patients who completed the program as scheduled was $44,800 and for the 16 who did not complete the entire program or who required additional therapy was $57,025.

Trippoli et al. conducted a meta-analysis of 5 clinical trials published between 1993 and 1996 with at least 100 patients with newly diagnosed untreated MM per treatment arm, and determined the cost-effectiveness ratio [158]. The trials included 4 comparing MP +/- IFNa and one comparing autologous BMT versus conventional chemotherapy. Survival data were abstracted and pooled (where more than 1 trial evaluated the treatment) from the published trial data and used to calculate the mean lifetime survival (MLS) for each therapy. Costs also were abstracted from the published literature of autologous transplantation and estimated at $60,000 (1995 US$) per patient, however a sensitivity analysis of the transplantation cost data used the range of $20,000 to $120,000 as the most extreme published values. Four of the clinical trials published cost data on MP as induction therapy, which averaged $2,700 per patient; no sensitivity analysis was performed for MP because of the high precision of these data.

The pooled MLS values for the MP versus MP plus IFNa were not significantly different (3.47 versus 3.74 years; $P > .05$). Autologous BMT had a significantly longer survival than the MP group (MLS 7.28 years; $P < .05$). The cost-effectiveness ratio was calculated by dividing the difference in costs between MP and BMT by the difference in life years gained (LYG) per patient. Using the $60,000 estimate for BMT, the cost per LYG (cost-effectiveness ratio [CER]) was $25,710 and ranged from $7,773 to $52,616 by the sensitivity analysis.

Sampson et al. identified from the literature 1 randomized controlled trial and 2 case series of high-dose therapy with autologous SCT versus conventional-dose chemotherapy as first-line treatment of MM [159]. Examined outcomes were LYG and event-free LYG. Cost estimates for SCT were based on out-of-area treatment costs for Central Sheffield University Hospitals and included costs for mobilization, stem cell harvest, 3-week inpatient hospital stay, outpatient follow-up, and pharmacy costs. The overall average treatment cost for SCT was £12,460 per patient. Cost estimates for conventional chemotherapy were based on the pharmacy costs of 6 to 9 courses of ABCM (Adriamycin, BCNU, cyclophosphamide, and MEL) and additional outpatient visit costs, yielding an average treatment cost of £1,980 per patient. The randomized trial data resulted in a mean 5-year survival benefit of 0.7 LYG for SCT patients, an additional 0.7 event-free LYG for SCT patients, and a CER of £14,970 per LYG. A sensitivity analysis using the case series data with information on 10-year survival rates determined the survival benefit to be 1.7 LYG and a CER of £6,160 per LYG. Fitting a mathematical Weibull curve to the survival data points yielded a 10-year survival benefit of 2.3 LYG, a CER of £4,553 per LYG, and a 20-year survival benefit of 3.8 LYG.

RESPONSE CRITERIA (METHODS TO DETECT MINIMUM RESIDUAL DISEASE)

Various techniques to measure biochemical or molecular tumor markers have been examined for their ability to detect minimum residual disease (MRD) in apheresis products, BM harvests, or in patients with MM pretransplantion and post-transplantation, and to predict prognosis. The most widely used method has been real-time polymerase chain reaction (PCR) to detect markers from the rearrangement of the immunoglobulin heavy chain (IgH) genes to idiotype specific sequences.

Two studies have reported that patients with MM whose apheresis products test positive for clonogenic IgH by PCR have significantly shorter PFS and OS [160-162]. Three studies have reported that there is no prognostic significance of detection of MRD by PCR [163-165]. Two studies demonstrated the percentage of tumor cells was significantly higher in BM harvests than in PBSC collections [166,167], whereas 1 study showed no difference in the percentage of tumor cells or CD34+ cells in leukapheresis products from the first versus second day of collection [168]. Two studies demonstrated that CD34+ selection of PBSC products significantly reduces the number of clonal cells by 2.15 logs [169] and by up to 3 logs [170], which corresponds to a reduction in the total quantity of tumor cells re-infused of 99.3% [169]. One study compared the detection of MRD by PCR versus immunofixation versus electrophoresis and determined that immunofixation was the only method that correlated with prognosis [171]. Another study noted that positive PCR detection of MRD significantly correlated with serum B2M level, but had only a marginal correlation with prognosis [172]. One study concluded there is no correlation between circulating clonal B cells and CD19+ cell count, and that the PB clonal cells were reduced after induction therapy but remained stable before and after PBSCT [173]. An additional study reported that clonotypic PBSCs are CD19+ B cells, and that the level of clonotypic cells decreases but persists after treatment [174]. Two studies reported that patients who received allogeneic transplants had a significantly higher rate of molecular CR determined by prospective PCR monitoring of MRD than patients who

received autologous transplants [175-177]. One study of allogeneic SCT patients demonstrated that 9 of 12 patients in clinical CR were also in molecular CR at a median of 6 months after transplantation [178]. One study provided a multicenter consensus strategy for detection of MRD and concluded that PCR is a more reproducible method than limiting dilution assays [179]. One study described the use of family-specific consensus probes instead of patient-specific idiotype sequences with real-time PCR for detection of MRD as a faster, reproducible, and less expensive method [180].

Other strategies have been investigated to detect MRD. Two studies noted a reduction in BM microvessel density (angiogenesis) after SCT, one associated the reduction with response to SCT and PFS [181] whereas the other found it was not prognostic of response to SCT [182]. One study determined that plasma cell morphology was prognostic of response to SCT and OS [183]. One study used an immunofluorescence technique to detect monoclonal plasma cells in PBSC apheresis products [184]. Patients who had relapsed disease at the time of leukapheresis had a significantly higher mean number of plasma cells and PB plasma cell labeling index in their products than patients collected in the plateau phase. One study compared 3 methods for estimating the BM plasma cell percentage: BM aspirate, core biopsy, and plasma cell labeling index [185]. There was a significant correlation between the 3 methods, and the highest estimate of BM plasma cell percentage as determined by the 3 methods was a significant predictor of CR, PFS, and OS.

One study assessed bone resorption by measuring urinary free pyridinoline (fPyr) and deoxypyridinoline (fDPyr), and assessed bone formation by measuring the serum concentrations of procollagen 1 extension peptide (P1CP) and bone-specific alkaline phosphatase (BSAP) [186]. Patients with elevated levels of fPyr, fDPyr, P1CP, and/or BSAP at the time of SCT had a normalization of their levels within a few months post-SCT, indicating a normalization of the abnormal bone turnover common in MM.

Several studies have used flow cytometry to quantitate malignant plasma cells or other markers. One used flow cytometry to quantitate and compare the number of malignant plasma cells in patients treated with conventional chemotherapy versus autologous PBSCT [187]. Patients treated with autologous PBSCT had a significantly reduced number of malignant plasma cells and patients with >30% normal plasma cells after treatment had significantly prolonged PFS (60 versus 34 months; $P = .02$). One study described the feasibility of using flow cytometry to measure myeloma-related antigens (B-B4 and CD38) as a method to detect aneuploid plasma cells in PBSC collections [188]. Another study used flow cytometry to detect plasma cells in apheresis products and demonstrated that immature plasma cells are polyclonal, whereas mature plasma cells are monoclonal [189].

Two studies have evaluated interphase fluorescence in situ hybridization (FISH) as a method to detect MRD. In one study, interphase FISH was able to detect abnormal plasma cells in the BM of 12/14 patients who had achieved a clinical CR after PBSCT (n = 11) or high-dose MEL without stem cell support (n = 3) [190]. In the other study, interphase FISH detected aneuploid cells in BM harvests that were prognostic of significantly shorter DFS (12 versus 23 months; $P = .009$) [191].

One study used flow cytometry to sort PB samples into CD19+, CD19-, and CD20+ fractions [192]. PCR was used to quantitate the number of CD19+ tumor cells in MM patients in remission post-PBSCT and found it to be similar to patients treated with standard-dose chemotherapy (VAD plus idarubicin), however, tumor cells detected in the CD19- fraction were significantly reduced in patients in remission post-PBSCT. In MM patients with progressive disease post-PBSCT, the number of tumor cells in the CD19+ and CD19- fractions was significantly higher than in remission patients post-PBSCT.

One study explored flow cytometry immunophenotyping using a panel of 21 monoclonal antibodies in a two-step gated procedure with DNA ploidy studies to detect MRD [193]. In BM samples from 61 patients with untreated newly diagnosed MM, 87% had an abnormal phenotype, 62% demonstrated DNA aneuploidy, and 95% had one or both techniques detecting abnormal plasma cells. Three months after autologous SCT, 29 PBSC and 19 BM samples were obtained. Abnormal plasma cells were detected in 44% of PBSC collections and 61% of BM samples.

FUTURE DIRECTIONS

Ongoing Studies

Several studies have been published in abstract form only, were recently completed, or are currently accruing patients but address critical issues that will affect the treatment recommendations made above. Maloney et al. described a feasibility trial of 32 patients treated with an autologous PBSCT followed by an allogeneic PBSCT from an HLA-identical sibling with a non-myeloablative conditioning regimen [194]. Attal et al. reported a multicenter randomized phase III trial of single versus tandem autologous PBSCT in 399 patients [195]. Segeren et al. conducted a multicenter randomized phase III trial of VAD followed by MEL (140 mg/m^2) without stem cell rescue versus VAD followed by Cy plus TBI and autologous PBSCT in 373 patients with previously untreated MM [196]. Blade et al. performed a multicenter randomized phase III trial comparing intensification therapy with 8 cycles of alternating BVMCP/VBAD versus autologous PBSCT with MEL (140 mg/m^2) plus TBI or MEL (200 mg/m^2) in 216 patients with MM treated with the same induction regimen [197]. Kropff et al. reported a randomized phase III trial of a standard (MEL 200 mg/m^2) versus intensive (MEL 200 mg/m^2 plus Cy 120 mg/kg plus idarubicin 42 mg/m^2) conditioning regimen for autologous PBSCT in 116 patients [198]. The final analyses of these trials in manuscript form with mature data will provide additional evidence that may change or add to the treatment recommendations.

Other studies that were recently closed or are still accruing patients include the following: (1) an SWOG/Eastern Cooperative Oncology Group/Cancer and Leukemia Group B–sponsored multicenter phase III randomized trial of VBMCP versus autologous PBSCT with MEL plus TBI conditioning as intensification therapy in patients with MM with stable or responding disease after induction therapy with VAD; patients

with at least a 75% cytoreduction after intensification undergo a second randomization of maintenance therapy with IFNa versus observation; and (2) an industry-sponsored, National Cancer Institute sponsored multicenter phase III randomized trial of MEL with or without a Holmium radiolabelled antibody as conditioning for autologous PBSCT; this study was closed due to late toxicity observed in the phase I/II patients and is being revised for further accrual.

Areas of Needed Research

After reviewing the evidence and highlighting the studies that are in progress, the panel recommends as the most important area of needed research the following: studies of post-response therapy to improve the quality of the response and extend survival. This includes studies of maintenance therapy of patients treated with autologous SCT, ie, posttransplantation maintenance studies comparing IFNa versus prednisone or thalidomide or its derivatives. Because there is no plateau in the survival curves post-autologous SCT for MM, this is the area most in need of improvement by further study.

DISCUSSION

In addition to the topics covered, we reviewed the evidence for PBSC mobilization regimens and timing of PBSC collections for autologous and allogeneic SCT. The panel concluded that there was not adequate evidence nor was this topic immediately relevant to the evaluation of outcomes after PBSCT, therefore, these sections were not included. We examined the evidence for vaccine therapy post-autologous SCT. These studies included too few patients to make a meaningful recommendation regarding this novel approach and also were excluded. The panel noted that although expert opinion has set an upper age limit of 70 years for autologous SCT, the decision for transplantation in the elderly population should be made on a case-by-case basis.

The authors recommend methodology standardization, including study design, analytical tests, and response criteria. Multicenter randomized phase III comparative trials with large enrollments and high statistical power are required in the US to advance the field more constructively than single institution phase II trials with one treatment arm. A standard set of response criteria, such as the International Bone Marrow Transplant Registry (IBMTR) MM response criteria, should be used for documentation of MM therapy responses. The expert panel also noted in the course of this review that the publication of preliminary analyses is often premature because a minimum of 3 to 5 years of follow-up is required before the survival curves start to separate due to the effect of posttransplantation salvage therapies. We advocate prompt reporting of mature data in full manuscript format. Abstracts do not adequately convey the full details of a clinical trial to meet evidence-based criteria for inclusion in systematic reviews, nor for making a true assessment of the widespread applicability or impact of the treatment outside the scope of the trial.

The treatment recommendations of this panel are based on the results of well-planned, scientifically sound, peer-reviewed clinical trials. All of today's current therapy for cancer is the result of the randomized clinical trial process. It is currently estimated that less than 5% of adults eligible to participate in cancer clinical trials actually enroll in a trial. The authors acknowledge the importance of third party payers in removing one barrier to participation in clinical trials by providing insurance coverage for the routine costs of care for patients enrolled in cancer clinical trials. We urge all carriers to extend benefits for participation in cancer clinical trials that is at least consistent with the scope of coverage defined by the Center for Medicare and Medicaid Services in the September 19, 2000 regulations to answer the critical treatment questions, not only for MM, but also for other malignant diseases.

LIMITATIONS OF THIS EVIDENCE-BASED LITERATURE REVIEW

There are limitations to any evidence-based review of the published literature. The criteria for this review included reliance only on published data, specifically peer-reviewed articles published since 1980. Unpublished data, which were not included in the review, usually represent "negative" findings and usually do not undergo peer review. We also excluded data published only in abstract form because they are usually not peer-reviewed and are presented in an abbreviated format.

Another limitation of this review is its reliance on published data rather than individual patient data. The stated goal of this review was to present evidence for making recommendations regarding the role of SCT in the therapy of MM. Time and financial constraints made it impractical to obtain data on individual patients from the large number of clinical trials included in this review. Although it was not the objective of this review to perform an extensive meta-analysis of individual patient data, such an analysis is warranted to further clarify the results of studies and address unanswered questions.

FUTURE INITIATIVES

This comprehensive, systematic review of the available evidence for the role of cytotoxic therapy with hematopoietic SCT in the therapy of MM is the second in a series of sequential articles sponsored by the American Society for Blood and Marrow Transplantation. Each review will summarize the evidence regarding the role of cytotoxic therapy with SCT in the treatment of a specific disease using defined methodology and grading criteria. The next review will address the role of SCT in the therapy of acute lymphoblastic leukemia (ALL).

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Appendix A. *Glossary of Terms*

ABCM	**Adriamycin, BCNU, cyclophosphamide, and melphalan**
ALL	**Acute lymphoblastic leukemia**
ANC	**Absolute neutrophil count**
B2M	**Beta$_2$-microglobulin**
BCNU	**Carmustine**
BM	**Bone marrow**
BMT	**Bone marrow transplantation**
BSAP	**Bone-specific alkaline phosphatase**
BVAP	**Carmustine (BCNU), vincristine, Adriamycin, and prednisone**
BVAPP	**Carmustine (BCNU), vincristine, Adriamycin, and prednisone plus alternate day prednisone between chemotherapy cycles**
CALGB	**Cancer and Leukemia Group B**
CCV	**Cyclophosphamide, carboplatin, and etoposide**
CER	**Cost-effectiveness ratio**
CHOP	**(intensified) Cyclophosphamide, Adriamycin, vincristine, and prednisone**
CI	**Confidence interval**
CM	**Cyclophosphamide and melphalan**
CMV	**Cytomegalovirus**
CR	**Complete response**
CRP	**C-reactive protein**
C-VAMP	**Cyclophosphamide, vincristine, Adriamycin, and methylprednisolone**
CVB	**Cyclophosphamide, etoposide, and carmustine (BCNU)**
Cy	**Cyclophosphamide**
d-TEC	**Dexamethasone, paclitaxel, Etoposide, and cyclophosphamide**
DAV	**Dexamethasone (orally days 1-4), Adriamycin (intravenous day 1), and vincristine (intravenous day 1)**
DCs	**Dendritic cells**
DFS	**Disease-free survival**
DLIs	**Donor lymphocyte infusions**
EBMT	**European Group for Blood and Marrow Transplantation**
ECOG	**Eastern Cooperative Oncology Group**
EDAP	**Etoposide, dexamethasone, cytosine arabinoside, and cisplatinum**
EFS	**Event-free survival**
fDPyr	**Urinary free deoxypyridinoline**
FISH	**Fluorescence in situ hybridization**
FFP	**Free(dom) from progression**
fPyr	**Urinary free pyridinoline**
G-CSF	**Granulocyte–colony stimulating factor**
GM-CSF	**Granulocyte-macrophage–colony stimulating factor**
GVHD	**Graft-versus-host disease**
HDS	**High-dose sequential**
HLA	**Human Leukocyte Antigen**
HRQoL	**Health-related quality-of-life**
IDM	**Intermediate-dose melphalan**
IFNa	**Interferon alpha**
Ig	**Immunoglobulin**
LCR	**Plasma cell light chain ratio**
LDH	**Lactate dehydrogenase**
LYG	**Life years gained**
M2	**BCNU, eldisine, cyclophosphamide, and melphalan**
MDS	**Myelodysplastic syndrome**
MEL	**Melphalan**
MLS	**Mean lifetime survival**
MM	**Multiple myeloma**
MP	**Melphalan and prednisone**
MPC	**Monoclonal plasma cells**
MRD	**Minimum residual disease**
NMSG	**Nordic Myeloma Study Group**
OS	**Overall survival**
P1CP	**Procollagen I extension peptide**
PBSC	**Peripheral blood stem cell**
PBSCT	**Peripheral blood stem cell transplantation**
PCR	**Polymerase chain reaction**
PFS	**Progression-free survival**
PR	**Partial response**
QALYs	**Quality adjusted life years**
RFS	**Relapse-free survival**
RSV	**Respiratory syncytial virus**

Appendix A. *(Continued)*

SC	**Stem cell**
SCF	**Stem cell factor**
SCT	**Stem cell transplantation**
SWOG	**Southwest Oncology Group**
TBI	**Total body irradiation**
TCR	**T-cell receptor**
TMI	**Total marrow irradiation**
TRM	**Treatment-related mortality**
TWiSTT	**Time without symptoms, treatment, or treatment toxicity**
VAD	**Vincristine (continuous infusion for 4 days), Adriamycin (continuous infusion for 4 days), and dexamethasone (orally, varying schedules)**
VAMP	**Vincristine, Adriamycin, and methylprednisolone**
VBMCP	**Vincristine, BCNU, melphalan, cyclophosphamide, and prednisone**
VCAD	**Vincristine, cyclophosphamide, Adriamycin, and dexamethasone**
VID	**Vincristine, idarubicin, and dexamethasone**
VC-VAMP	**Verapramil, cyclophosphamide, vincristine, Adriamycin, and methylprednisolone**
VMCP	**Vincristine, melphalan, cyclophosphamide, and prednisone**
VMCPP	**Vincristine, melphalan, cyclophosphamide, and prednisone plus alternate day prednisone between chemotherapy cycles**
WBC	**White blood cell**

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Appendix B. *Outline of Article*